

FEDERATION PROCEEDINGS

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CONTENTS

NO 1, PART I, FEBRUARY 1946

Program of Thirtieth Annual Meeting, Atlantic City, 1946

1

PART II

Abstracts of papers in Physiology	1
Abstracts of papers in Biochemistry	118
Abstracts of papers in Pharmacology	161
Abstracts of papers in Pathology	217
Abstracts of papers in Nutrition	228
Abstracts of papers in Immunology	244
Index of Subjects	257

NO 2, JUNE, 1946

Abstracts Received Too Late For Preceding Issue	263
Abstracts, Correction of Errors in	265
Atlantic City Meeting, Notes on	266
Symposium on Applications of the Newer Knowledge of Nutrition to Present Day Problems	
The Food and Nutrition Board of the National Research Council	
A Review of Some of Its Accomplishments and a Forecast of its Future	267
International Food Evaluation Activities and Problems	270
Nutritional Aspects of the Milk Supply	273
Human Dietary Allowances	277
The Significance and Limitations of Food Composition Tables	280
Symposium on Advances in Pharmacology Resulting from War Research	
Therapeutic Applications of Chemical Warfare Agents	285
Insecticides and Rodenticides	292
Chemotherapy of Malaria, 1941-45	298
Bacterial Chemotherapy	304

NO 3, SEPTEMBER, 1946

Donald Russell Hooker	313
Reports Submitted by Secretaries of the Constituents Societies	314
Symposium on Physiological Contributions to War Problems	
Introduction	318
High Altitude Problems in Aviation	319
Effects of Acceleration in Relation to Aviation	327
Clothing and Heat Exchanges	344
Problems of Visual Physiology During the War	351
Physiological Contributions to the Problem of Shock	354
Symposium on Some Recent Trends in Neurospora Biochemistry	
Introduction	361
Neurospora as a Biochemical Tool	362
The Application of Neurospora to Bioassay	366
Adenine-Requiring Mutants of Neurospora crassa	370
Enzyme Studies on a Temperature Sensitive Mutant of Neurospora	376
Altered Sulfonamide Antagonism in Neurospora	379
Symposium on Biochemistry of Malarial Parasites	
Introduction	390
Enzyme Systems Operating within the Malarial Parasite	390
Chemical and Nutritional Observations on Malarial Parasites Grown <i>in Vitro</i>	397
Metabolism of the Malarial Parasite	400
The Influence of Naphthoquinones upon the Respiratory and Carbohydrate Metabolism of Malarial Parasites	406

Survey of Physiology in North America, 1915

Introduction	407
Section I Purposes and Methods of the Study	108
Section II The Identification and Analysis of the North American Population of Physiologists	417
Section III Economics	422
Section IV The Careers and Incentives of Physiologists	123
Section V Future Physiology	132

No 1, DECEMBER, 1916

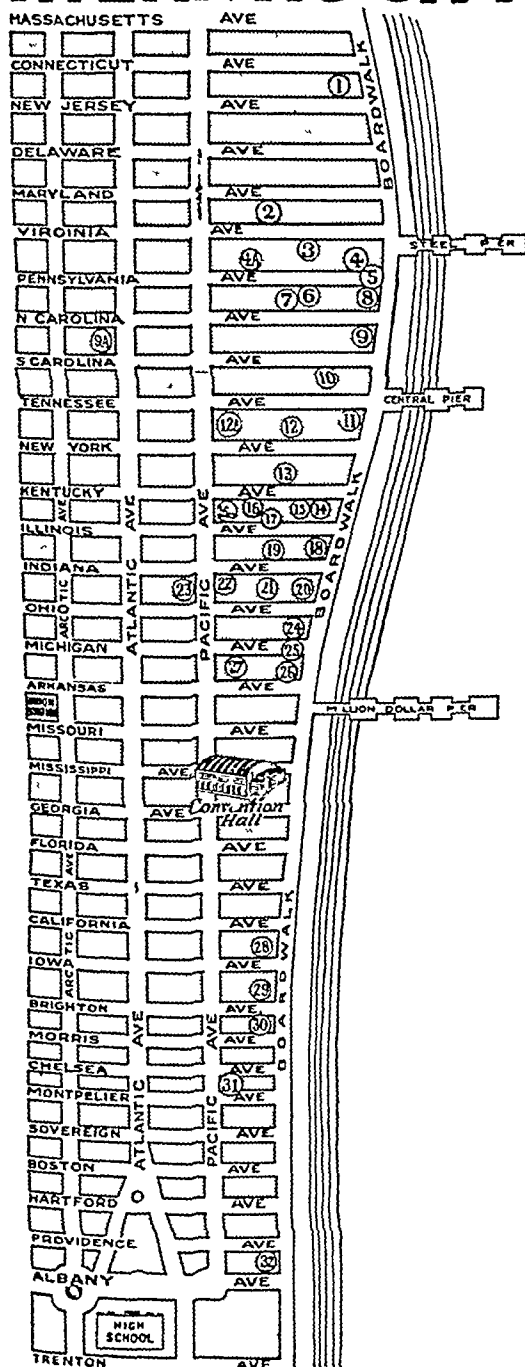
Reports Submitted by Secretaries of the Constituent Societies	137
Annual Meeting, Chicago 1917	138
Donald Russell Hooker	139
Executive Committee 1917	440
Former Executive Committees	440
Federation By-Laws	443
Placement Service	444
The American Physiological Society	444
The American Society of Biological Chemists	448
The American Society for Pharmacology and Experimental Therapeutics	453
The American Society for Experimental Pathology	456
The American Institute of Nutrition	459
The American Association of Immunologists	461
Membership List of All Societies	463
Summary of Membership	537
Deceased Members	537
Regulations for the Preparation of Abstracts	540
Index	542

FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY

PROGRAM 1946

Atlantic City, March 11, 12, 13, 14, 15

ATLANTIC CITY



Map Numbers refer to hotels (1) Breakers, (2) Franklin Inn, (3) Morton, (4) Seaside, (4A) Holmhurst, (5) Strand, (6) Colton Manor, (7) Lafayette, (8, 9) Chalfonte-Haddon Hall, (9A) Penn-Atlantic, (10) Senator, (11) Mayflower, (12) Flanders, (12A) Columbus, (13) Monticello, (14) Sterling, (15) Jefferson, (16) Kentucky, (16A) Byron, (17) Madison, (18) Traymore, (19) Brighton, (20) Claridge, (21) Runnymede, (22) Crillon, (23) Eastbourne, (24) Marlborough-Blenheim, (25) Dennis, (26) Shelburne, (27) Arlington, (28) Ritz Carlton, (28A) Fox Manor, (29) Ambassador, (30) Chelsea, (31) Villa D'Este, (32) President Streets are thirteen blocks to the mile

GENERAL INFORMATION

The first post-war Federation meeting was planned to be held in Cleveland but when the ODT lifted the ban on convention travel the Local Committee found it impossible to secure requisite commitments. Efforts were then made to obtain facilities in New York, Chicago, Philadelphia, St. Louis and Baltimore. These failed. Arrangements were finally made for the meeting in Atlantic City under the sponsorship of a Philadelphia Local Committee. The Local Committee regrets that the expense of attending the meeting must be somewhat higher than heretofore.

The Federation will meet in Atlantic City March 11, 12, 13, 14, 15, 1946. Scientific and business meetings will be held Tuesday, Wednesday, Thursday and Friday. Monday will be devoted to Council and Executive Committee meetings and to registration.

All of the essential functions will be centralized in the Municipal Convention Hall. This includes Federation headquarters, registration, section meetings, symposia and motion picture demonstrations. The Headquarters will be in Room 8, registration in the Entrance Lobby, symposia in the Ball Room, and section meetings as indicated in the program. By action of the Federation Executive Committee the customary Federation joint session, banquet and static demonstrations will be omitted.

Registration will open at 9:00 A.M. on Monday, March 11 in the Entrance Lobby of the Convention Hall. Members of any of the constituent societies and interested physicians, students or workers in biological laboratories may register. A registration fee of \$2.00 will be required. Admittance to the scientific sessions will be restricted to those who

- 10 Harry D Kingsley (*introduced by* Herman S Wigodsky), *Randolph Field*
Effects of abrupt deceleration on the electrocardiogram (Lead II) in the cat in the supine position

PHYSIOLOGY B

Tuesday, 9 00 a m

COMMITTEE ROOM 21

Brain Metabolism

- 1 Antoine Rémond (*by invitation*), P W Davies (*by invitation*) and D W Bronk, *University of Pennsylvania*
Influence of the vascular bed on the pattern of oxygen tension in the cerebral cortex
- 2 D W Bronk, M G Larrabee and P W Davies (*by invitation*), *University of Pennsylvania*
The rate of oxygen consumption in localized regions of the nervous system in pre-synaptic endings and in cell bodies
- 3 J F Fazekas (*introduced by* E B Astwood), *Tufts Medical College*
Cerebral metabolism of hyperthyroid, thyroid-deficient and cretinous rats
- 4 Shirley Ferris (*by invitation*) and Harold E Himwich, *Albany Medical College*
The effect of age on the hypoglycemic depletion of glycogen in the central nervous system
- 5 Frederic A Gibbs, Harry P Maxwell (*by invitation*) and Erna L Gibbs (*by invitation*), (with the technical assistance of Ruth E Hurwitz), *University of Illinois*
Volume flow of blood through the brain of man at rest, during hyperventilation and while breathing high CO₂
- 6 S S Kety (*by invitation*) and C F Schmidt, *University of Pennsylvania*
Effects of alterations in the arterial tensions of carbon dioxide and oxygen on cerebral blood flow and cerebral oxygen consumption of normal young men
- 7 W E Stone, J E Webster (*by invitation*), J Kopala (*by invitation*) and E S Gurdjian (*by invitation*), *Wayne University and Grace Hospital*
Effects of carbon dioxide administration on cerebral metabolism in hypoxia
- 8 Williamina A Himwich (*by invitation*), Edmund Homburger (*by invitation*), Robert Maresca (*by invitation*), and Harold E Himwich, *Albany Medical College*
Brain metabolism in unanesthetized and anesthetized man
- 9 Harold E Himwich, Edmund Homburger (*by invitation*), Benjamin Etsten (*by invitation*), Robert Maresca (*by invitation*), George

York (*by invitation*), and Williamina A Himwich (*by invitation*), *Albany Medical College*

Effect of pentothal anesthesia on canine cerebral cortex

- 10 W F Windle and A V Jensen (*by invitation*), *Northwestern University*

Brain structure after intermittent exposure to simulated high altitudes

PHYSIOLOGY C

Tuesday, 9 00 a m

ROOM C

Gastro-intestinal Tract

- 1 Warren S Rehm, *University of Louisville*
Evidence that the major portion of the gastric potential originates between the submucosa and mucosa
- 2 W B Youmans and Lynn Foltz (*by invitation*), *University of Oregon*
Correlation of electrical and mechanical events in the intestinal lumen of unanesthetized dogs
- 3 H Necheles, L Walker (*by invitation*) and Wm Olson (*by invitation*), *Michael Reese Hospital, Chicago*
A gradient of gastro-intestinal motility following hemorrhage
- 4 David W Northup and Edward J Van Liere, *West Virginia University*
The effect of chloral hydrate on the gastric emptying time in man
- 5 F R Steggerda, R K Richards, and Justin Hoekstra (*by invitation*), *University of Illinois and Abbott Laboratories*
Observations on the synergistic effects of various antispasmodic compounds and nembutal on colon activity in normal adult males
- 6 M I Grossman (*by invitation*) and A C Ivy, *Northwestern University*
Prevention of ulcer in Mann-Williamson dogs by the oral administration of intestinal extracts
- 7 S C Harris (*by invitation*) and A C Ivy, *Northwestern University*
The influence of extrinsic gastro-intestinal innervation on dextroamphetamine induced anorexia
- 8 Hugo Krueger, *University of Tennessee*
Relationships between changes in muscle length, tone, tension, and pressure
- 9 J Kaulbersz, T L Patterson, D J Sandweiss and H C Saltzstein (*by invitation*), *Wayne University and Harper Hospital*
Endocrine glands and gastric secretion

- 10 Franklin Hollander and Frances U Lauber (by invitation), Mount Sinai Hospital, New York

Calcium in gastric mucus

- 11 Leonard D Kurtz (by invitation) and Byron B Clark, Albany Medical College

The inverse relationship of the secretion of hydrochloric acid to the tension of carbon dioxide in the stomach (Pharmacology)

- 12 M H F Friedman, I J Pincus (by invitation) and J Earl Thomas, Jefferson Medical College

The influence on gastric secretion of fluids introduced into the intestine

- 13 Eric Ogden and Frank D Southard, Jr (by invitation), Universities of Texas and of California

The influence of wine on gastric acidity

- 9 S M Horvath and D Tebbie (by invitation), Harvard University and Boston City Hospital

The phosphates and other compounds in the gastrocnemius muscle of scorbutic guinea pigs

- 10 Jay Tepperman and Oscar Bodansky (by invitation), Edgewood Arsenal

Effect of P-Aminopropiophenone induced methemoglobinemia on the oxygenation of working muscle in human subjects

- 11 Clara Torda and Harold G Wolff, Cornell University Medical College

Effect of serum and its fractions on acetylcholine synthesis

- 12 Saul L Cohen (introduced by Robert Gesell), University of Michigan

Some relationships in the response of rectus abdominus muscle to acetylcholine and potassium

PHYSIOLOGY D

Tuesday, 9 00 a m

Room D

Muscle

- 1 Alexander Sandow, Washington Square College
The causation of the latency relaxation
- 2 P W Davies (introduced by D W Bronk), University of Pennsylvania
Rapid bursts of oxygen consumption in stimulated muscle
- 3 Dugald Brown and H Claire Lawler (by invitation), New York University
The activation of myosin-atpase by pressure in the presence of calcium
- 4 S W Kuffler, (introduced by Dr R W Gerard), University of Chicago
The muscle membrane during contracture
- 5 A J Kosman (by invitation) and S L Osborne, Northwestern University
Frequency-intensity curves of normal, denervated and recovering gastrocnemii of the dog
- 6 J E Markee and H Lowenbach (by invitation), Duke University
The delimitation of separately innervated regions of single skeletal muscles
- 7 Ernst Fischer and Virginia W Ramsey (by invitation), Medical College of Virginia
Changes in muscle proteins during atrophies of various types and the retardation of some of these changes by electrical treatment
- 8 S Spiegelman and M D Kamen (introduced by H B Steinbach), Washington University School of Medicine
The site of uncoupling of phosphorylation from carbohydrate metabolism in the presence of NaN_3

PHYSIOLOGY A

Tuesday, 2 00 p m

COMMITTEE ROOM 20

Circulation

- 1 A T Miller Jr, University of North Carolina
Analysis of the Normal T-1824 Disappearance Curve
- 2 Antonio Ramirez and Dina B Rappaport (introduced by Hampden Lawson), University of Louisville
Determination of the circulating cell volume by a partial washout method
- 3 David T Overbey (introduced by Hampden Lawson), University of Louisville
The recruitment of blood from the spleen during hemorrhage
- 4 Edwin L Smith (by invitation), B W Haynes (by invitation), and E I Evans, Medical College of Virginia
The effect of sympathectomy and tilting on arterial blood pressure, cardiac output and right atrial pressure in man
- 5 David F Opdyke, Western Reserve University
Circulatory failure induced by partial cerebral ischemia
- 6 W C Levin (by invitation), Griff T Ross (by invitation), Raymond Echols (by invitation), and Raymond Gregory, University of Texas
The mechanism of the fall in arterial pressure produced by high spinal anesthesia in patients with essential hypertension
- 7 Paul A Nicoll and R L Webb (by invitation), Indiana University and University of Chicago

Intermittency of blood flow in peripheral fields

- 8 A. B. Hertzman, W. C. Randall and K. E. Jochim, *St. Louis University*
The quantitation of cutaneous vascular reactions with the photoelectric plethysmograph
- 9 Keith S. Grimson, *Duke University*
Studies of the central or reflex control of the circulation several years after sympathectomy
- 10 R. E. Forster, II, B. G. Ferris, Jr., and R. L. Day (introduced by H. C. Bazett), *Climatic Research Laboratory, Lawrence*
The relationship in the hand between total heat exchange and blood flow at various ambient temperatures
- 11 Edward J. Van Liere and David F. Marsh (by invitation), *West Virginia University*
Action of certain autonomic agents on the blood pressure rise produced in dogs by acute oxygen lack

7 30 p m Business meeting

PHYSIOLOGY B

Tuesday, 2 00 p m

COMMITTEE ROOM 21

Adrenals

- 1 Elaine P. Rall, *New York University*
The effect of calcium pantothenate on survival in adrenalectomized rats
- 2 Frank A. Hartman and Jonathan S. Thatcher (by invitation), *Ohio State University*
A sodium retaining substance of the adrenal
- Dwight J. Ingle and Elizabeth A. Oberle (by invitation), *Upjohn Company, Kalamazoo*
The effect of adrenalectomy in rats on urinary non-protein nitrogen during forced-feeding and during fasting
- 4 Lena A. Lewis (by invitation) and Irvine H. Page, *Cleveland Clinic Foundation*
Method of assaying adrenal preparations for protective action against toxic material (typhoid vaccine)
- 5 Sheppard M. Walker (by invitation) and A. S. Gilson, Jr., *Washington University*
The response of the *triceps surae* of the adrenalectomized and normal rat to single and multiple stimulation
- 6 Clifford A. Angerer, *Ohio State University*
The respiration of nerves and arteries of adrenalectomized rats
- 7 J. Gonzalez Q. (by invitation) and Clifford A. Angerer, *Ohio State University*
The respiration of erythrocytes of adrenal-

ectomized rats in the presence of various extracts

- 8 M. L. Pabst, R. L. Sheppard, M. H. Kulzenga (introduced by D. J. Ingle), *The Upjohn Company, Kalamazoo, Michigan*
Comparative effects of adrenal cortex hormones on hepatic glycogen deposition and muscle-work performance
- 9 A. Leimdorfer, R. Arana and M. Hack (introduced by W. S. McCulloch), *University of Illinois*
A central action of adrenalin in raising blood sugar
- 10 Douglas E. Smith (introduced by F. A. Hartman), *Ohio State University*
Adrenal function following ovariectomy in the rat
- 11 George Sayers and Marion A. Sayers (introduced by Louis S. Goodman), *University of Utah*
Regulation of pituitary adrenocorticotrophic activity (*Pharmacology*)
- 12 Marion A. Sayers (introduced by Louis S. Goodman), *University of Utah*
A method for the assay of adrenocorticotrophic hormone (*Pharmacology*)

7 30 p m Business meeting

PHYSIOLOGY C

Tuesday, 2 00 p m

Room C

Central Nervous System

- 1 Ernst Gellhorn and James F. Bosma (by invitation), *University of Minnesota*
Electromyographic observations under conditions of stimulation of the motor cortex
- 2 John E. Scarff and James L. Pool (introduced by Fred A. Mettler), *Columbia University*
Reflex activity in the lower extremities after verified transection of the spinal cord in man
- 3 Janice Robinson (by invitation) and W. Horsley Gantt, *Johns Hopkins University*
The cardiac component of the orienting reflex
- 4 William F. Allen, *University of Oregon*
Effects of destroying three localized temporal lobe areas on correct conditioned differential responses of the dog's fore leg from general cutaneous stimuli
- 5 R. F. Becker, R. A. Groat and W. F. Windle, *Northwestern University*
Study of learning and memory in guinea pigs suffering brain concussion
- 6 L. A. Crandall, Jr. and T. S. Hill (by invitation), *University of Tennessee*

- Cardiovascular and respiratory responses to emotion in psychopathic subjects and controls
- 7 James E P Toman, Ewart A Swinyard (*by invitation*), and Louis S Goodman, *University of Utah*
Some properties of maximal electroshock seizures
- 8 Harry Grundfest, *Columbia University*
The origin of electrical activity from spinal afferent stimulation of the inferior olive of cats
- 9 R M E Carrea (*introduced by* Fred A Mettler), *Columbia University*
Physiologic effects of bilateral cerebellar removals in the primate
- 10 Fred A Mettler, *Columbia University*
The experimental production of static tremor
- 11 Janet Travell and Nolton H Bigelow (*introduced by* McKen Cattell), *Cornell University Medical College*
Referred somatic pain does not follow a simple "Segmental" pattern
- 12 H T Wycis (*by invitation*) and E A Spiegel, *Temple University Medical School*
Further studies of cortical and retinal influences upon vestibulo-ocular reflexes
- 7 30 p m Business meeting
- 6 John MacLeod and William H Summerson (*by invitation*), *Cornell University Medical College*
The phosphatase activity of human spermatozoa
- 7 Norman M Keith and Arnold E Osterberg (*by invitation*), *Mayo Clinic*
The human tolerance for potassium
- 8 M H Jacobs and Dorothy R Stewart (*by invitation*), *University of Pennsylvania*
Some ionic and osmotic equilibria of the erythrocyte
- 9 Walter S Wilde, Dean B Cowie (*by invitation*) and Louis B Flexner, *Carnegie Institution of Washington*
The permeability of the placenta to radioactive ions
- 10 H J Curtis and J D Teresi (*by invitation*), *Oak Ridge, Tennessee*
Activation of tissue elements by slow neutron exposure
- 11 L V Heilbrunn, *University of Pennsylvania*
Heat death, heat injury and toxic factor
- 12 Matilda Moldenhauer Brooks, *University of California*
Mechanism of fertilization of eggs
- 13 C I Reed and Norman R Joseph (*by invitation*), *University of Illinois*
In vitro examination of synovial dynamics with a needle electrode

PHYSIOLOGY D

Tuesday, 2 00 p m

Room D

General Physiology

- 1 Thomas F Anderson (*introduced by* D W Bronk), *University of Pennsylvania*
The activation of bacterial viruses by aromatic amino acids
- 2 Charles O Warren and Franklin G Ebaugh, Jr (*by invitation*), *Cornell University Medical College*
Some factors influencing the anaerobic glycolysis of rat liver
- 3 Samuel R Tipton and W L Nixon (*by invitation*), *Medical College of Alabama*
The effect of thioracil administration on the succinioxidase and cytochrome oxidase of rat liver
- 4 Irvin M Korr, *New York University*
The relation between tissue metabolism and physiological activity
- 5 Kenneth C Fisher and Florence H Armstrong (*by invitation*), *University of Toronto*
The oxygen consumption concerned with growth in *E coli* and the effect of sulfathiazole and n propyl carbamate on it

7 30 p m Business meeting

PHYSIOLOGY A

Wednesday, 9 00 a m

COMMITTEE ROOM 20

Synaptic Mechanisms

- 1 John C Finerty (*by invitation*) and Robert Gesell, *University of Michigan*
The rôle of intra and extracellular cH in neurohumoral stimulation
- 2 Charles R Brassfield, and Elwood T Hansen (*by invitation*), *University of Michigan*
Acid effects of ammonium compounds
- 3 Robert Gesell, E T Hansen (*by invitation*) and Jeane Siskel (*by invitation*), *University of Michigan*
Further observations on humoro electrotonic nature of stimulation, inhibition, summation and after-discharge of nerve cells
- 4 Jeane Siskel (*by invitation*) E T Hansen (*by invitation*) and Robert Gesell, *University of Michigan*
Interplay of half-centers
- 5 C Heymans, R Pannier, and R Verbeke (*introduced by* Philp Bard), *University of Gand, Belgium*

- Influence of anticholinesterase (prostigmin), atropine and acetylcholine on the cardiovascular and respiratory centers
- 6 A van Harreveld, *California Institute of Technology, Pasadena*
Depolarisation in the spinal cord caused by asphyxiation
- 7 Gordon M Schoepfle, *Washington University*
Synaptic delay and central inhibition in relation to electrotonic potentials
- 8 George W Stavaky, *University of Western Ontario*
The action of adrenaline and acetylcholine on partially isolated neurones of the central nervous system
- 9 M G Larrabee and D W Bronk, *University of Pennsylvania*
Afterdischarge from sympathetic ganglion cells following preganglionic nerve stimulation
- 10 Birdsey Renshaw, *Rockefeller Institute for Medical Research and Oberlin College*
Interaction of nerve impulses in the gray matter as a mechanism in central inhibition
- 11 Francis M Forster, Winslow J Borkowski and Robert H McCarter (introduced by M H F Friedman), *Jefferson Medical College*
Depression of the cerebral cortex induced by applications of acetylcholine

PHYSIOLOGY B

Wednesday, 9 00 a m

COMMITTEE ROOM 21

Circulation

- 1 Philip Dow, P F Hahn (by invitation), and W F Hamilton, *University of Georgia School of Medicine and University of Rochester*
The simultaneous transport of T-1824 and radioactive red cells through the heart and lungs
- 2 Isaac Starr, *University of Pennsylvania*
Abnormal forms of the ballistocardiogram
- 3 J L Nickerson, *Columbia University*
Determinations of cardiac output in the dog by the ballistic method
- 4 W F Hamilton and John W Remington, *University of Georgia School of Medicine*
Comparison of the time concentration curves in arterial blood of dye injected at a constant rate with that of dye injected intravenously
- 5 John W Remington and W F Hamilton, *University of Georgia School of Medicine*
Calculation of the arterial uptake and stroke volume from the pressure pulse contour
- 6 Kenneth E Jochim, *St Louis University School of Medicine*

- A mathematical analysis of pulse volume determinants
- 7 A N Taylor and H J Ralston (introduced by Eric Ogden), *University of Texas and College of Physicians and Surgeons, San Francisco*
The axial stream in the aorta of dogs and cats
- 8 H D Bruner (by invitation), and C F Schmidt, *University of Pennsylvania*
Blood flow in the bronchial artery of the anesthetized dog
- 9 S S Sobin (introduced by L M Landis), *Harvard Medical School*
Accuracy of indirect determinations of blood pressure in the rat Relation to temperature of the plethysmograph and width of cuff
- 10 Eugene M Landis, *Harvard Medical School*
The electroosmotic transport of fluid through the walls of injured capillaries
- 11 W D Collings, Eric Ogden and A N Taylor (by invitation), *University of Texas Medical School*
Plasma renin substrate levels during adrenal insufficiency

PHYSIOLOGY C

Wednesday, 9 00 a m

Room C

Aviation Problems

- 1 T E Boyd and John M Brookhart (by invitation), *Loyola University School of Medicine*
The influence of the pericardium on effective venous pressure
- 2 John M Brookhart (by invitation) and T E Boyd, *Loyola School of Medicine*
The circulatory effects of local variations in intra-thoracic pressure
- 3 J B Bateman, *Mayo Aero Medical Unit*
Intrapulmonary mixing curves and the detection of abnormal ventilation
- 4 John S Gray and Earl L Green (by invitation), *Randolph Field*
The measurement of voluntary ventilation capacity
- 5 D R Drury, J P Henry (by invitation), P O Greeley, Irene Klain (by invitation) and Eli Movitt (by invitation), *University of Southern California*
The effect of continuous and of intermittent pressure breathing on kidney function
- 6 W V Whitehorn, (by invitation), Abraham Edelmann, (by invitation) and Fred A Hitchcock, *Ohio State University*
Cardiovascular responses to explosive decompression

- 7 Abraham Edelmann (*by invitation*), W V Whitehorn (*by invitation*), and Fred A Hitchcock, *Ohio State University*
The effects of explosive decompression on human subjects
- 8 Fred A Hitchcock, Abraham Edelmann (*by invitation*), Frederick F Shelden (*by invitation*) and W V Whitehorn (*by invitation*), *Ohio State University*
The volume and composition of air expelled from the lung during explosive decompression
- 9 A P Gagge and H M Sweeney, *Wright Field*
A practical criterion for evaluating the danger of explosive decompression
- 10 W O Fenn, L E Chadwick, H Rahn, and A B Otis (*by invitation*), *University of Rochester*
A new method of representing alveolar air concentration
- 11 A Otis (*by invitation*), H Rahn, M Epstein (*by invitation*), and W O Fenn, *University of Rochester*
Performance as related to composition of alveolar air
- 12 H Rahn, A Otis (*by invitation*), and W O Fenn, *University of Rochester*
The Pressure—Volume diagram of the thorax and lung

PHYSIOLOGY D

Wednesday, 9 00 a m

Room D

Thyroid and Pancreas

- 1 W P VanderLaan and A Bissell (*introduced by E B Astwood*), *Tufts Medical School and Joseph H Pratt Diagnostic Hospital*
Influence of thyrotropin on iodine metabolism in the thyroid glands of hypophysectomized rats
- 2 Walter Fleischmann, *Johns Hopkins School of Medicine*
Effect of thyroxin on estrogen-induced changes in fowl
- 3 William T Salter and Wallace F White (*by invitation*) and E A McKay (*by invitation*), *Yale University*
The lymphatic conveyance of thyroid hormone
- 4 S B Barker, *State University of Iowa*
Absence of dinitro cresol effect in thiouracil-treated rats
- 5 K E Paschkis, A Cantarow and E K Tillson (*by invitation*), *Jefferson Medical College and Hospital*

Further studies on inhibition of cytochrome oxidase by thiouracil in thyroid and bone marrow

- 6 Albert J Dalton, Harold P Morris (*by invitation*), Celia Dubnik (*by invitation*) *National Institute of Health*
Changes in the thyroid and other organs in mice receiving thiouracil (*Pathology*)
- 7 R Levine, Clarence Cohn (*by invitation*), and Samuel Soskin, *Michael Reese Hospital*
The influence of sugar and other metabolites on the respiratory exchange of eviscerated normal and depancreatized dogs
- 8 Williamina A Himwich (*by invitation*) and Harold E Himwich, *Albany Medical College*
Organic phosphates and insulin
- 9 James A Greene, *Baylor University*
Effect of additional carbohydrate intake without altered insulin dosage upon oxidation of dextrose by subjects with controlled diabetes mellitus
- 10 Piero P Foà, Jay A Smith (*by invitation*) and H Weinstein (*by invitation*), *Chicago Medical School*
The effect of insulin on blood cocarboxylase
- 11 David F Waugh, *Massachusetts Institute of Technology*
Reactions involved in insulin fibril formation

PHYSIOLOGY A

Wednesday, 2 00 p m

COMMITTEE ROOM 20

Heart

- 1 Maurice B Visscher and Allan Hemingway, *University of Minnesota*
The turbulent flow factor in cardiac work
- 2 R E Sturm (*by invitation*) and E H Wood, *Mayo Aero Medical Unit*
An instantaneously recording cardiographometer
- 3 A Sidney Harris, *Western Reserve University*
Ventricular fibrillation and standstill in coronary occlusion, anoxia and hemorrhage
- 4 L N Katz, W Wise (*by invitation*), J Meyer (*by invitation*), B Lendrum (*by invitation*) and K Jochim, *Michael Reese Hospital*
Mechanical efficiency of the heart in experimental heart failure
- 5 Jane Sands Robb, *Syracuse University*
A study of Q-T interval in various species
- 6 George C Henny, Bert R Boone and W Edward Chamberlain (*introduced by Morton J Oppenheimer*), *Temple University School of Medicine*
The electrokymograph an apparatus for recording motion (for example, that of the heart shadow border)

- 7 Bert R Boone (*by invitation*), Fred G Gillick (*by invitation*), W Edward Chamberlain (*by invitation*) and Morton J Oppenheimer, *Temple University School of Medicine*
Electrokymograms of heart border motion principles of record interpretation
- 8 Fred G Gillick (*by invitation*), Bert R Boone (*by invitation*), George C Henny (*by invitation*) and Morton J Oppenheimer, *Temple University School of Medicine*
The electrokymograph application as a photo-electric plethysmograph
- 9 H F Helmholz, Jr (*introduced by F C Mann*), *Mayo Foundation*
Response of blood pressure and pulse rate of the new born rat to changes in body temperature
- 10 Robert W Lackey (*by invitation*) and Carl A Bunde, *Southwestern Medical College*
The relationship between blood ketone levels and the storage of glycogen by the heart in acute experiments

PHYSIOLOGY B

Wednesday, 2 00 p m

COMMITTEE ROOM 21

High Altitudes

- 1 S Rodbard, *Army Air Force*
The effect of oxygen, altitude, and exertion on breath-holding time
- 2 F G Hall, *Wright Field*
Respiratory efficiency at altitude
- 3 Robert D Dripps (*by invitation*) and Julius H Comroe, Jr, *University of Pennsylvania*
The respiratory and circulatory response of normal man to 100, 18, 16, 14, 12, 10 and 8% O₂
- 4 F R Blood (*by invitation*) and F E D'Amour, *University of Denver*
Physiology of the rat at high altitudes
- 5 G A Millikan, *University of Pennsylvania*
Speed of response of arterial oxygen saturation to rapid change in equivalent altitude
- 6 L F Nims, L L Langley (*by invitation*) and R W Clarke, *Yale University*
Anoxia, carbon dioxide and liver glycogen
- 7 Louise H Marshall (*introduced by Heinz Specht*), *National Institute of Health*
Respiratory water loss at ground level and altitude
- 8 J P Henry, Irene Klain, Eli Movitt and J P Meehan (*introduced by P Greely*), *University of Southern California*
The effects of anoxia on the capillary permeability of the human arm
- 9 J C Lilly (*introduced by D W Bronk*), *University of Pennsylvania*

Studies on the mixing of gases within the respiratory system with a new type nitrogen meter

- 10 J W Wilson (*by invitation*), F G Hall and H G Swann, *Wright Field*
Physiological effects of high negative mask pressures during simulated free fall
- 11 Ludwig G Lederer and George J Kidera (*by invitation*), *Pennsylvania-Central and United Air Lines*
Hyperpneic tetany in commercial aircraft passengers
- 12 D W Lund and J H Lawrence (*introduced by Laurence Irving*), *University of California*
Studies on the cause of pain in high altitude "bends"
- 13 J Clifford Stickney, *West Virginia University*
The effect of various degrees of intermittent anoxia on body weight loss in normal rats

PHYSIOLOGY C

Wednesday, 2 00 p m

Room C

Special Senses

- 1 S S Stevens, *Harvard University*
The two basic mechanisms of sensory discrimination
- 2 J E Hawkins, Jr, H Davis and M H Lurie (*by invitation*), *Harvard Medical School*
Injury of the inner ear produced by exposure to loud tones
- 3 H Davis, C T Morgan, J E Hawkins, Jr, R Galambos and F W Smith (*by invitation*), *Harvard Medical School*
Temporary hearing-loss following exposure to loud tones
- 4 Theodore C Ruch and Harry D Patton (*by invitation*), *Yale University*
The relation of the deep opercular cortex to taste
- 5 Harry D Patton (*by invitation*), Theodore C Ruch and John F Fulton, *Yale University*
The relation of the foot of the pre- and post-central gyrus to taste in the monkey and chimpanzee
- 6 Herbert S Wells, *University of Minnesota*
Effects of temperature gradients on the intensity, duration and thresholds of experimental traumatic pain
- 7 Grace M Roth, Dan Y Burrill (*by invitation*), and A C Ivy, *Northwestern University*
The effect of histamine, administered intravenously in increasing concentration, on the pain threshold of normal subjects
- 8 N Kleitman and A Ramsaroop (*by invitation*) *University of Chicago*
Body temperature and cutaneous sensitivity to tingling and pain

PHYSIOLOGY D

Wednesday, 2 00 p m

Room D

Endocrines

- 1 James H Leatham, *Rutgers University*
The influence of testosterone propionate on the plasma proteins of hypothyroid rats
- 2 M M Hoffman and M L Desbarats (*introduced by I S L Browne*), *McGill University*
Metabolism of dehydroisoandrosterone
- 3 W H Perlman (*by invitation*) and Gregory Pincus, *Clark University*
The metabolism of pregnenolone
- 4 Oscar Hechter (*by invitation*) and Gregory Pincus, *Worcester Foundation for Experimental Biology*
The 17-ketosteroids in plasma, urine and sweat
- 5 Gregory Pincus, Zareh Hadidian and Mary Yeaton (*by invitation*), *Worcester Foundation for Experimental Biology*
A comparative study of androgen and 17-ketosteroid excretion in men
- 6 M Marks (*by invitation*), H T Wycis (*by invitation*) and E A Spiegel, *Temple University Medical School*
Anticonvulsant effect of pregnenolone
- 7 M C Chang (*introduced by G Pincus*), *Worcester Foundation for Experimental Biology*
Number of spermatozoa required for the fertilization of superovulated eggs in the rabbit
- 8 Carl G Heller (*by invitation*), Edwin C Jungck (*by invitation*) Warren O Nelson, and Helen A Winter (*by invitation*), *Oregon, Iowa, and Columbia Universities*
Gonad-pituitary relationship—metabolism of pituitary gonadotrophins by ovaries transplanted into the spleen
- 9 A E Rakoff (*by invitation*) and J H Leatham, *Jefferson Medical College and Rutgers University*
Clinical gonadotropic therapy complicated by antihormone formation
- 10 Herbert C Stoerk (*introduced by H P Smith*), *Columbia University*
Thymic atrophy (accidental involution) and its failure to occur in calcium deficiency (*Pathology*)
- 11 Hans Selye and Helen Stone (*by invitation*), *University of Montreal*
Effect of the diet upon the renotropic, nephrosclerotic, cardiotropic and adrenotropic actions of crude anterior pituitary preparations

- 12 Richard C deBodo and Kathryn F Prescott (*by invitation*), *New York University College of Medicine*
The water exchange of diabetes insipidus dogs under varying nutritional and hydration conditions

Physiology Editorial Conference

Wednesday 7 50 p m

CONFERENCE ROOM NO 15 AT
CONVENTION HALLA C Ivy, *Chairman*

Members interested in publication affairs are cordially invited to attend

Physiological Survey Committee
Partial Report

Wednesday, 9 00 p m

COMMITTEE ROOM 20

Philip Bard, *Chairman*

- 1 Objectives of the survey General summary
Some Practical Results
E F Adolph
- 2 Population structure of physiologists in North America
Philip Dow
- 3 The economics of physiologists
T E Boyd
- 4 The careers and incentives of physiologists
J H Comroe, Jr
- 5 Specific questions to the committee
- 6 General discussion, the committee listening

All interested are invited to attend

PHYSIOLOGY A

Thursday 9 00 a m

COMMITTEE ROOM 20

Estrogens

- 1 Herbert G Birch (*by invitation*) and George Clark, *Yerkes Laboratories, Florida*
The mechanism of estrogen induced changes in dominance-subordination relationships in the female chimpanzee
- 2 George Clark and Herbert G Birch (*by invitation*), *Yerkes Laboratories, Florida*
The effect of sex hormones on the dominance-subordination relationships of the castrate female chimpanzee
- 3 Arthur A Hellbaum and Roy O Greep, *University of Oklahoma*
The stimulating action of estrogen on release of luteinizing hormone (*Pharmacology*)

- 4 Szego, Clara M and Sidney Roberts (*introduced by Hudson Hoagland*), *Worcester Foundation for Experimental Biology*

The nature of circulating estrogen

- 5 Jae L Littrell (*by invitation*), John Tom (*by invitation*) and Carl G Hartman, *University of Illinois*

Use of the immature guinea-pig for estrogen assay

- 6 Isolde T Zeckwer, *University of Pennsylvania*
The passage of endogenous estrogen across the parabiotic union in rats

- 7 Henry C Hill, Jr (*introduced by G S Ladie*), *Duke University School of Medicine*

The influence of diethylstilbestrol on the systolic blood pressure of normal rats

11 00 a m Business meeting

PHYSIOLOGY B

Thursday, 9 00 a m

COMMITTEE ROOM 21

Nutrition

- 1 Gladys R Bucher (*introduced by R Hafkesbrung*), *Women's Medical College*
Variations in uropepsin elimination due to diet

- 2 J F McClendon and Wm C Foster (*by invitation*), *Hahnemann Medical College*
Concentric zones of distribution of fluorine in milk and dental caries

- 2 Victor A Drill and Carroll A Pfeiffer (*by invitation*), *Yale University*
Relation of B vitamins, inanition and methionine to inactivation of estrone by liver

- 4 D Bailey Calvin and Edgar J Poth (*by invitation*), *University of Texas*
The oral administration of protein hydrolysates

- 5 Leon L Miller (*introduced by G H Whipple*), *University of Rochester*
Dog hemoglobin parenterally well utilized to maintain weight and nitrogen balance
Utilization improved by dl-methionine but not by dl-isoleucine

- 6 Smith Freeman, Tsan-wen Li (*by invitation*) and Chi Che Wang (*by invitation*), *Northwestern University*
Experimental production of uremia in dogs by protein depletion

11 00 a m Business meeting

PHYSIOLOGY C

Thursday, 9 00 a m

ROOM C

Vision

- 1 A Chapanis (*introduced by L A Pinson*), *Wright Field*

The dark adaptation of the color anomalous

- 2 Ernest A Pinson and A Chapanis (*by invitation*), *Wright Field*

The relationship between measures of night vision and dark adaptation

- 3 Charles Sheard, *Mayo Foundation and Mayo Clinic*

The effects of smoking on the dark adaptation of rods and cones

- 4 Theodore Louis Jahn, *State University of Iowa*
The kinetics of visual processes III Dark Adaptation

- 5 G Walsh (*by invitation*), H Barlow (*by invitation*), and H I Kohn, *Massachusetts Institute of Technology and Harvard Medical School*

Magnetic stimulation of the human retina

- 6 Alfred F Bliss (*introduced by H E Himwich*), *Albany Medical College*

Photolytic lipids from visual pigments

- 7 Mary Ishimoto (*by invitation*) and George Wald, *Harvard University*

Phospholipids in the visual cycle

11 00 a m Business meeting

PHYSIOLOGY D

Thursday, 9 00 a m

ROOM D

Exercise

- 1 John Hald and Winfrey Wynn (*by invitation*), *Emory University*

Observations on work capacity, work performance, and certain metabolic processes when strenuous exercise was taken after isocaloric meals of low and high carbohydrate content

- 2 Peter V Karpovich, *Randolph Field*

Relation between breath holding and endurance in running, and the Harvard step-up test score

- 3 Louise H Ray (*by invitation*), George B Ray (*deceased*) and J Raymond Johnson, *Long Island College of Medicine*

A method for determining reduction time of cutaneous blood, and its significance in relation to certain physiological changes

- 4 J Raymond Johnson, George B Ray (*deceased*) and Louise H Ray (*by invitation*), *Long Island College of Medicine*
Reduction time of peripheral cutaneous blood as a means of evaluating fitness
- 5 Frederic T Jung, Lillian E Cisler (*by invitation*) and Velma C Miller (*by invitation*), *Northwestern University and Passavant Memorial Hospital*
Certain influences affecting the cardiac recovery index of medical students
- 6 Raymond A Weiss (*by invitation*) and Peter V Karpovich, *Randolph Field*
Variability in the energy cost of standard exercises
- 7 H S Mayerson, *Tulane University*
The use of carbon dioxide in preventing post-exercise orthostatic circulatory insufficiency

11 00 a m Business meeting

PHYSIOLOGY A

Thursday, 2 00 p m

COMMITTEE ROOM 20

Shock

- 1 Samuel Gelfan, *Columbia University*
Sensitivity to morphine during recovery from hemorrhagic shock
- 2 S C Wang, *Columbia University*
Additional evidence on the afferent nervous factor in experimental traumatic shock
- 3 A C Corcoran and Irvine H Page, *Cleveland Clinic Foundation*
Crush syndrome (post traumatic anuria)
- 4 Harold C Wiggers and Raymond C Ingraham, *University of Illinois*
Continuous intravenous infusion of alkalinizing agents during impending hemorrhagic shock conditions
- 5 Carl J Wiggers, David F Opdyke and J Raymond Johnson, *Western Reserve University*
Portal pressure gradients in hemorrhagic shock
- 6 Ewald E Selkurt, *Western Reserve University*
Renal blood flow and renal clearance during hemorrhagic shock
- 7 Robert W Ramsev and Terrine K Adler (*by invitation*), *University of Rochester*
Some local processes concerned in the genesis of traumatic shock
- 8 Jose Manrique (*introduced by Carl J Wiggers*), *Western Reserve University*
Electrocardiographic changes in hemorrhagic and ischemic compression shock

- 9 Raymond C Ingraham and Harold C Wiggers, *University of Illinois*
Treatment of impending hemorrhagic shock with an antihistamine agent
- 10 Harold D Green, J Maxwell Little and J E Hawkins, Jr, *Bowman Gray, School of Medicine*
Further observations on the toxic factor in ischemic compression shock
- 11 William R Amberson, C Martin Rhode (*by invitation*) and Joye J Jennings (*by invitation*), *University of Maryland*
Clinical experience with hemoglobin saline solutions
- 12 Victor Schenker (*by invitation*), J A F Stevenson (*by invitation*) and J S L Browne, *McGill University and Royal Victoria Hospital*
The characteristic pattern of changes in nitrogen metabolism after trauma
- 13 W A Andreae (*by invitation*), Victor Schenker (*by invitation*) and J S L Browne, *McGill University Clinic and Royal Victoria Hospital*
Riboflavin metabolism after trauma and during convalescence in man
- 14 R A Phillips and P B Hamilton (*by invitation*), *Rockefeller Institute for Medical Research*
Duration of renal ischemia required in dogs to produce damage of lethal degree
- 15 G E Wakerlin (*with the technical assistance of T Lefco and H Minatoya*), *University of Illinois College of Medicine and Parke, Davis and Co*
The effect of unilateral renal artery constriction on the renin content of the contralateral kidney

PHYSIOLOGY B

Thursday, 2 00 p m

COMMITTEE ROOM 21

Kidney

- 1 Alfred Gilman, Frederick S Philips (*by invitation*) and Ethel S Koelle (*by invitation*), *Edgewood Arsenal*
The renal clearance of thiosulfate in the dog
- 2 J P Maes and R P Forster (*by invitation*), *Dartmouth Medical School*
The effects of blood pressure changes, reflexly induced, on glomerular activity and renal plasma flow in the unanesthetized rabbit
- 3 R P Forster (*by invitation*) and J P Maes, *Dartmouth Medical School*
Renal function in the rabbit as influenced by the administration of water, anesthetics and diuretics

- 4 J Maxwell Little, J E Hawkins, Jr and Harold D Green, *Bowman Gray School of Medicine*

Diuresis resulting from intravenous infusion of urine

- 5 B E Lowenstein (*by invitation*), A C Corcoran and Irvine H Page, *Cleveland Clinic Foundation*

Determination of renal function in rats

- 6 A V Wolf (*introduced by* H W Himwich), *Albany Medical College*

The retention and excretion of continuously administered intravenous salt solutions in man

- 7 R F Pitts and W D Lotspeich (*by invitation*), *Cornell University Medical College*

The renal excretion and reabsorption of bicarbonate

- 8 Edwin P Hiatt and Virginia Suhrie (*by invitation*), *North Carolina School of Medicine*

Renal excretion of cinchona alkaloids and some quaternary base derivatives and their effect on renal hemodynamics

- 9 W G Kubicek and F J Kottke (*introduced by* M B Visscher), *University of Minnesota*

Glomerular filtration and renal plasma flow during renal and splanchnic nerve stimulation in dogs in relation to arterial hypertension

- 10 Nathan W Shock, *National Institute of Health*

Age changes in kidney function of human subjects

- 11 Sigwin B Raska (*introduced by* Charles O Warren), *Cornell University Medical College*

The metabolism of the kidney in experimental renal hypertension

PHYSIOLOGY C

Thursday, 2 00 p m

ROOM C

Temperature Regulation

- 1 E F Adolph and G W Molnar (*by invitation*), *University of Rochester*

Temperature gradients in men exposed to cold

- 2 G W Molnar (*by invitation*) and E F Adolph, *University of Rochester*

Heat exchanges of man in cold outdoor environments

- 3 H S Belding, H D Russell (*by invitation*) and R C Darling, *Harvard University*

Factors maintaining heat balance of the clothed man at different grades of activity in the cold

- 4 H D Russell (*by invitation*), H W Belding, and R C Darling, *Harvard University*

Physiological reactions of men working in the cold in relation to the amount of clothing worn

- 5 Walter C Randall, *St Louis University School of Medicine*

Enumeration of functional sweat glands in the human

- 6 S D Gerking (*by invitation*) and Sid Robinson, *Indiana University*

Decline in the rates of sweating of men working in severe heat

- 7 Sid Robinson and S D Gerking (*by invitation*), *University of Indiana*

Thermal balance of men working in severe heat

- 8 John F Hall, Jr (*introduced by* A P Gagge), *Wright Field*

The thermal (copper) in man—a new instrument for the study of radiation and convection heat loss in man

- 9 Walter B Shelley (*by invitation*) and Steven M Horvath, *Fort Knox, Kentucky*

Acclimatization of men to high temperatures

- 10 John P Marbarger (*by invitation*) and Craig L Taylor, *Wright Field*

The effect of air movement on human response to heat and humidity

- 11 Craig L Taylor and John P Marbarger (*by invitation*), *Wright Field*

Some effects of extreme heat and humidity on man

PHYSIOLOGY D

Thursday, 2 00 p m

ROOM D

Central Nervous System

- 1 Harlow W Ades and David L Raab (*by invitation*), *Emory University*

Studies on the corpus callosum and anterior commissure of monkeys

- 2 John L Hampson (*by invitation*), Clinton R Harrison (*by invitation*) and Clinton N Woolsey, *Johns Hopkins University*

Somatotopic localization in the cerebellum

- 3 H T Chang (*by invitation*), T C Ruch and A A Ward, Jr (*by invitation*), *Yale University*

Representation of muscles in the motor cortex of the macaque

- 4 Clinton N Woolsey, *Johns Hopkins University*

Comparative studies on dual somatic afferent areas in cerebral cortex of rabbit, cat, dog, pig, sheep and monkey

- 5 Arthur A Siebens (*by invitation*) and Clinton N Woolsey, *Johns Hopkins University*

Cortical autonomic center for the eyes on the mesial surface of the frontal lobe in cat

- 6 S A Talbot, C N Woolsey, J M Thompson
(*by invitation*), *Johns Hopkins University*
Visual areas I and II of cerebral cortex of
rabbit
- 7 E A Spiegel and N P Scala (*by invitation*),
Temple University School of Medicine
Influence of the superior colliculus upon the
vestibulo ocular reflex
- 8 Allen D Keller, *Baylor University College of
Medicine*
The striking inherent tonus of the deafferented
central pupilloconstrictor neurons
- 9 Hans Lowenbach and Ian Barbour (*introduced
by F D McCrea*), *Duke University*
An automatic device for continuous frequency
analysis of electroencephalograms
- 10 M A Lennox (*by invitation*), T C Ruch, and
B Guterman (*by invitation*), *Yale University*
The effect of benzedrine and other chemical
agents upon the post convulsive (electric
shock) EEG
- 11 A R McIntyre, A L Dunn (*by invitation*), and
P E Tullar (*by invitation*), *University of
Nebraska College of Medicine*
The effect of d-tubocurarine on the electrical
activity of dogs' brains
- 12 Chester W Darrow, Julian Pathman (*by invitation*), and Warren Morse (*by invitation*),
Institute for Juvenile Research, Chicago
Autonomic significance of "Blocking" and
"Facilitation" in Electroencephalogram

PHYSIOLOGICAL CONTRIBUTIONS TO WAR PROBLEMS

H C Bazett, *University of Pennsylvania*,
Chairman

Friday, 9 00 a m

BALL ROOM

- 1 A C Ivy, *Northwestern University*
High altitude problems in aviation
- 2 E J Baldes, *Mayo Aero Medical Unit*
The effects of acceleration in relation to
aviation
- 3 A C Burton, *University of Western Ontario*
Clothing and heat exchange
- 4 K Hartline, *University of Pennsylvania*
Visual problems
- 5 M I Gregersen, *Columbia University*
Shock

PHYSIOLOGY A

Friday, 1 30 p m

COMMITTEE ROOM 20

Respiration

- 1 F S Grodins, Allen Lein (*by invitation*), and
Harry F Adler, *Randolph Field*

Changes in the acid-base balance of the blood
during asphyxia

- 2 H Schwerma (*by invitation*), A C Ivy, A E
Sidwell, Jr (*by invitation*), W Wolman (*by
invitation*) and H Feldman (*by invitation*),
Northwestern University

A comparative study of the methods for re-
suscitation from carbon monoxide asphyxia

- 3 I Arthur Mirsky, E Lipman (*by invitation*)
and Roy R Grinker (*by invitation*), *Michael
Reese Hospital*

Breath-holding time in anxiety states

- 4 Edgar C Black and Virginia S Black (*by in-
vitation*), *Dalhousie University*

Oxygen and CO₂ dissociation curves of the
blood of the Atlantic salmon *Salmo salar*
salar Linnaeus acclimated to winter tem-
peratures

- 5 Morton Galdston and John A Luetscher, Jr
(*introduced by Jav Tepperman*) *Johns Hop-
kins Hospital*

Oxygen and carbon dioxide tensions in arterial
blood and alveolar air at rest and after ex-
ercise in healthy subjects and in patients
exposed to phosgene

- 6 Vivian G Behrmann (*introduced by Robert
Gesell*), *Henry Ford Hospital*

Continuous blood oxygen saturation in intra-
venous barbiturate anesthesia

- 7¹ Richard G Horton (*introduced by Boris B
Rubenstein*), *Edgewood Arsenal*

Fatal doses and respiratory minute volumes in
rabbits intravenously injected continuously
with NaCN

- 8 A W Hetherington and R A Miller (*by invitation*), *Randolph Field*

The effect of intravenous nitrogen on the
respiration and circulation of the cat

PHYSIOLOGY B

Friday, 1 30 p m

COMMITTEE ROOM 21

Nutrition

- 1 Max Kleiber, *University of California*
Survival time and metabolic rate of starving
rats
- 2 Ancel Keys, *University of Minnesota*
Experimental human starvation—general and
metabolic results of a loss of one fourth the
body weight in six months
- 3 Josef Brozek (*introduced by Ancel Keys*), *Uni-
versity of Minnesota*
Changes in specific gravity and body fat of
young men under conditions of experimental
semi-starvation
- 4 Olaf Mickelsen (*introduced by Ancel Keys*),
University of Minnesota

PAPERS READ BY TITLE

PHYSIOLOGY

- The urinary excretion of thiamine, pyrimin (the pyrimidine-like component of thiamine) and riboflavin by man in semi-starvation
- 5 Ernst Simonson, *University of Minnesota*
Electrocardiographic changes in semi-starvation
 - 6 Austin Henschel, *University of Minnesota*
The deterioration of brief endurance work capacity during semi-starvation
 - 7 Henry Longstreet Taylor, *University of Minnesota*
The effect of six months of semi-starvation on the maximal oxygen intake
 - 8 Chandler McC Brooks and David N Marine (by invitation), *Johns Hopkins*
A study of oxygen consumption in obesity
 - 9 L Willard Freeman, Arthur Loewy (by invitation) and Victor Johnson, *University of Chicago*
Physiologic icterus of the newborn

PHYSIOLOGY C

Friday, 1 30 p m

Room C

Nerve

- 1 Joseph Erlanger and Gordon M Schoepfle, *Washington University*
Studies in nerve degeneration and regeneration
- 2 R Beutner and T C Barnes, *Hahnemann Medical College*
The origin of the spike potential in nerve
- 3 A Rosenblueth and J Garcia Ramos (by invitation), *Instituto Nacional de Cardiologia de Mexico*
Changes of nerve properties near a killed region
- 4 R G Grenell and H S Burr (by invitation), *Yale University*
D C potentials and ulnar nerve dysfunction
- 5 R A Groat and H Koenig (by invitation), *Northwestern University*
Centrifugal course of functional deterioration in motor nerve deprived of circulating blood
- 6 D Nachmansohn, *Columbia University*
On the rôle of acetylcholine during nerve activity
- 7 Charles H Sawyer (introduced by J E Markee), *Duke University*
Cholinesterases in peripheral nerve fibers
- 8 A M Shanes (introduced by D E S Brown), *New York University College of Dentistry*
The action of sulfanilamide on the resting potential of frog nerve

- 1 Shannon C Allen and A P Gagge, *Acro Medical Laboratory, Wright Field*
The ability of anaesthetized human subjects to breathe against continuous pressure
- 2 Evelyn Anderson, Joseph A Long (by invitation) and Erna Lindner (by invitation), *University of California*
Studies on the perfusion of the isolated pancreas factors influencing insulin production
- 3 T C Barnes and M D Amoroso (by invitation), *Hahnemann Medical College*
A method of scoring a patient's electroencephalogram in deep breathing giving a cerebral hyperventilation index
- 4 T C Barnes and R Beutner, *Hahnemann Medical College*
Electrical activity of acetylcholine compared with choline, acetate, phosphate, potassium and other substances associated with nerve activity
- 5 T C Barnes and I Mauer (by invitation), *Hahnemann Medical College*
Bioelectrical studies of fatigue I Recovery of fatigued polarized muscle by reversal of the poles of the galvanic current
- 6 T C Barnes and H Brieger (by invitation), *Hahnemann Medical College*
Bioelectrical studies of fatigue II Student's electroencephalograms taken at 8 a m and 5 p m
- 7 T C Barnes, H S Ruth (by invitation), and E K Hultzman (by invitation), *Hahnemann Medical College*
Electroencephalography of infants under pentothal
- 8 Joseph Hall Bodine, *State University of Iowa*
Uric acid formation in the developing egg of the grasshopper *Melanoplus differentialis*
- 9 J M Bookhart (introduced by W F Windle), *Northwestern University*
Mechanical factors in the production of spinal cord injury by gunshot wounds to the vertebrae
- 10 Chandler McC Brooks, *Johns Hopkins University*
Activity and the development of obesity
- 11 H D Bruner and W E Stephens (introduced by C F Schmidt), *University of Pennsylvania*
Trial of the thermistor as a means of estimating blood flow
- 12 W E Burge, *University of Illinois*
Shift from negative to positive brain potential in the human during general anesthesia

- 13 A Cantarow, A E Rakoff (by invitation), and K E Paschkis, *Jefferson Medical College*
Studies of stilbestrol monomethyl ether
- 14 William G Clark, I D R Gardiner (by invitation), A K McIntyre (by invitation), and Helen Jorgenson (by invitation), *University of Southern California*
The effect of positive acceleration on fluid loss from blood to tissue spaces in human subjects on the centrifuge
- 15 William G Clark, I D R Gardiner (by invitation), A K McIntyre (by invitation) and Helen Jorgenson (by invitation), *University of Southern California*
Effect of hyperglycemia and insulin hypoglycemia on man's tolerance to positive acceleration
- 16 Savino A D'Angelo (introduced by Harry A Charipper), *Wright Field and Washington Square College*
The respiratory exchange in human subjects during prolonged exposures to moderately low simulated altitudes
- 17 Savino A D'Angelo (introduced by Harry A Charipper), *Wright Field and Washington Square College*
Urine volume and phosphorus excretion in human subjects during prolonged exposure to moderately low simulated altitudes
- 18 Chester W Darrow, Julian Pathman (by invitation) and Warren Morse (by invitation), *Institute for Juvenile Research, Chicago*
Autonomic and electroencephalographic effects of posture
- 19 John Emerson Davis, *University Arkansas*
Hyperchromic anemia produced in dogs by choline and carbamyl choline
- 20 Richard C deBodo and David Marine, *New York University and Montefiore Hospital*
The change in the water metabolism and in the endocrine glands of long surviving diabetes insipidus dogs
- 21 E C del Pozo, *Instituto Politecnico Nacional, Mexico*
Inhibitory responses of pregnant cat's uterus to epinephrin and hypogastric stimulation
- 22 Joseph C Franklin, Harold Guetzkow and Josef Brozek (introduced by Ancel Keys), *University of Minnesota*
Changes in postural steadiness and pulse rate after short vigorous exertion
- 23 M H F Friedman and Wm J Snape (by invitation) *Jefferson Medical College*
Color changes in the mucosa of the colon in children is affected by food and psychic stimuli
- 24 E Gellhorn and H M Ballin (by invitation), *University of Minnesota*
Water intoxication and the electroencephalogram
- 25 Maunis Godbey (by invitation), Norma M Hajek (by invitation) and H M Hines *State University of Iowa*
Changes in muscle and nerve during prolonged reflex hypertonus and contracture
- 26 Albert S Gordon, *New York University*
Antihormone reactions to blood, urinary and pituitary gonadotrophins
- 27 Albert S Gordon, with the assistance of Bernard Bernstein (by invitation), *New York University*
The adrenal gland and phagocytosis in the spleen
- 28 A Graybiel, D I Hupp and J L Patterson, Jr (introduced by J L Lahenthal, Jr), *U S Naval Air Station, Pensacola, Florida*
The law of the otolith organs
- 29 Paul O Greeley, Helen Jorgenson (by invitation), William G Clark, D R Drury, and J P Henry (by invitation), *University of Southern California*
Effect of anoxia on man's tolerance to positive acceleration
- 30 Harold Guetzkow (by invitation), Austin Henschel and Josef Brozek (by invitation), *University of Minnesota*
Relationship of "psychoneurotic" changes to carbohydrate utilization in men on experimentally varied intake of B complex vitamins
- 31 E S Gurdjian (by invitation) and W E Stone, *Wayne University College of Medicine and Grace Hospital*
Cerebral lactic acid and phosphates in concussion
- 32 C C Guthrie, *University of Pittsburgh*
Cause and prevention of a type of leg deformity in brooder raised chicks
- 33 George Hallenbeck (by invitation), Jack Glazier (by invitation) and George Maison, *Wright Field*
Radar measurement of rates of free fall of anthropomorphic dummies and man
- 34 J E Hawkins, Jr, Harold D Green, and J Maxwell Little, *Bowman Gray School of Medicine*
Hypotensive reactions to cross transfusion in dogs
- 35 Austin Henschel and Angie Mae Sturgeon (by invitation), *University of Minnesota*
The effect of semi starvation on the emptying of the human stomach
- 36 Austin Henschel, Henry Longstreet Taylor and Ancel Keys, *University of Minnesota*
The recovery of capacity for physical performance following experimental malaria in man
- 37 C Heymans, R Pannier and A Van Ostende (introduced by Philip Bard), *University of Gand, Belgium*

- Influence of overventilation on the cardiovascular reflexes of carotid sinus origin
- 38 Hudson Hoagland, Gregory Pincus, Fred Elmadjian (*by invitation*), Worcester Foundation for Experimental Biology
Stressful psychomotor performance and adrenal cortical function in man
- 39 Justin Hoekstra (*by invitation*) and F R Steggerda, University of Illinois
The effects of the antihistamine compound pyribenzamine on colonic activity in unanesthetized dogs
- 40 C S Houston (*introduced by* J L Lilienthal, Jr), U S Naval Air Station, Pensacola, Florida
Relation of pulmonary ventilation to arterial oxygen saturation
- 41 Theodore Louis Jahn, State University of Iowa
The kinetics of visual processes I Critical flicker frequency as a function of intensity
- 42 Theodore Louis Jahn, State University of Iowa
The kinetics of visual processes II Brightness discrimination and visual acuity as functions of intensity
- 43 A V Jensen (*by invitation*), R F Becker and W F Windle, Northwestern University
Effect of intermittent exposure to a simulated altitude of 30,000 feet on memory in guinea pigs
- 44 Geoffrey Keighley (*by invitation*) and William G Clark, California Institute of Technology and University of Southern California
Flicker fusion frequency thresholds during positive acceleration
- 45 R Krouse (*by invitation*), G C Wickwire (*by invitation*) and W E Burge, University of Illinois
Warm-up period in physical exercise in relation to brain potential
- 46 C D Leake, University of Texas
Physiological Standards
- 47 Tsan-wen Li (*by invitation*) and Smith Freeman, Northwestern University
The effect of inhaled methyl disulphide on liver fat of rats
- 68 Tsan-wen Li (*by invitation*) and Smith Freeman, Northwestern University
The effect of inhaled methyl disulphide on benzene poisoning in dogs
- 49 J L Lilienthal, Jr, and R L Riley (*by invitation*), U S Naval Air Station, Pensacola, Florida
The relationship of alveolar and arterial oxygen tension
- 50 P L MacLachlan (*introduced by* Dr E J VanLiere), West Virginia University
Effect of anoxic anoxia on stomach emptying time of rats fed corn oil
- 51 J F McClendon, Hahnemann Medical College
A slide rule for pH of indicators and buffers and for bicarbonate equilibria
- 52 David I Macht, Sinai Hospital, Baltimore
Comparison of opiates, demerol, and cobra venom on cats' pupils
- 53 David I Macht, Sinai Hospital, Baltimore
Pharmacodynamic reactions of previously irradiated organisms
- 54 David I Macht, Sinai Hospital, Baltimore
Thromboplastic properties of mercurial diuretics
- 55 David I Macht, Sinai Hospital, Baltimore
Influence of snake venoms on prothrombin time of normal and hemophilic blood
- 56 David I Macht, and Marcus Ostro (*by invitation*), Sinai Hospital, Baltimore
Experimental detoxification of pemphigus blood
- 57 W G Moss (*introduced by* G E Wakerlin), University of Illinois
Vitamin A levels of dog plasma
- 58 W G Moss (*by invitation*) and G E Wakerlin, University of Illinois
Vitamin K and experimental renal hypertension
- 59 N Nelson (*by invitation*), L W Eichna (*by invitation*), W B Shelley (*by invitation*), and S M Horvath, Fort Knox, Kentucky
The effect of air movement on the loss of heat by evaporation, convection, and radiation from nude and clothed individuals
- 60 E Pardo (*by invitation*), J Derbez (*by invitation*) and E C del Pozo, Universidad Nacional de Mexico
Cihuapahtli, an activator of uterine motility
- 61 T L Peele (*by invitation*), R A Groat and W F Windle, Duke University Medical School
Reactions of the spinal cord to laminectomy
- 62 R F Pitts and W D Lotspeich (*by invitation*), Cornell University Medical College
Factors determining pH and titratable acid of the urine
- 63 C I Reed and B P Reed (*by invitation*), University of Illinois
X-ray studies on bone
- 64 R Rhines (*by invitation*), H W Magoun and W F Windle, Northwestern University Medical School
The bulbar inhibitory mechanism in concussion
- 65 R L Riley (*by invitation*) and J L Lilienthal, Jr, U S Naval Air Station, Pensacola, Florida
The indirect determination of partial pressures in alveolar air

- 66 S Rodbard, *Michael Reese Hospital*
Factors affecting bubble volume in the tissues at various altitudes
- 67 L W Roth (by invitation), R K Richards and F R Steggerda, *Abbott Laboratories*
Inhibition of the emetic effect of intravenous glutamic acid in dogs
- 68 Ernest C Siegfried (by invitation) and John W Bean, *University of Michigan*
Degenerative changes induced in the CNS of albino rats by exposure to O at high pressure
- 69 Ernst Simonson and Josef Brozek (by invitation), *University of Minnesota*
Maximum speed of movement as a test of muscle function in different nutritional states
- 70 Franklin F Snyder, *Harvard University*
The effect of pentobarbital sodium upon the resistance to asphyxia in the newborn
- 71 E Spiegel and M Spiegel-Adolph (by invitation), *Temple University School of Medicine*
Loss of righting reflexes in experimental cerebral concussion
- 72 S Spiegelman (introduced by H B Steinbach), *Washington University, School of Medicine*
The inhibition of enzyme formation
- 73 S Spiegelman, M D Kamen, and Reba Dunn (introduced by H B Steinbach), *Washington University School of Medicine*
Mechanism of azide inhibition of synthetic activity and its relation to phosphorylation
- 74 Mitzi I Suskind (by invitation), Norma M M Hajek (by invitation), and H M Hines, *State University of Iowa*
The effect of massage upon denervation atrophy of skeletal muscle
- 75 James E P Toman and E A Swinyard (by invitation), *University of Utah*
A comparison of time relations in convulsive and nonconvulsive responses to cortical stimulation
- 76 G E Wakerlin, H Minatoya (by invitation), and T Lefco (by invitation), *University of Illinois*
Additional observations on the prophylaxis of experimental renal hypertension with renal extracts
- 77 G E Wakerlin, Wayne Donaldson (by invitation) and Oliver Kamm (by invitation), *University of Illinois*
Treatment of experimental renal hypertension with hog renal extract fractions
- 78 G E Wakerlin, Wayne Donaldson (by invitation) and Oliver Kamm (by invitation), *University of Illinois*
Treatment of experimental renal hypertension with beef and sheep renal extracts
- 79 G E Wakerlin, T Lefco (by invitation), and H Minatoya (by invitation), *University of Illinois*
The effect of unilateral nephrectomy on the development and maintenance of experimental renal hypertension
- 80 K G Wakim, *Indiana University*
The effects of ethyl alcohol on the isolated heart
- 81 K G Wakim, *Indiana University*
The influence of ergotovine on survival time of rats in shock
- 82 Herbert S Wells, *University of Minnesota*
Effects of thermal gradients and thermal equalization on latent pain and hyperalgesia resulting from injury
- 83 Samuel M Wells (by invitation), Ancel Keys, Austin Henschel, Henry Longstreet Taylor and Olaf Mickelsen (by invitation), *University of Minnesota*
Liver function in malaria
- 84 Clinton N Woolsey, Francis M Dick (by invitation) and Robert H Frantz (by invitation), *Johns Hopkins University*
Electrical responses in gyrus cinguli evoked by electrical stimulation of ipsilateral mammillary body in cat and monkey
- 85 Majorie B Zucker (introduced by M I Gregeren), *Columbia University*
Studies on spontaneous hemostasis, with evidence for a humoral factor

BIOCHEMISTRY A

Tuesday, 9 00 a m

(See Bulletin Board for location)

Carbon Compounds and Carbon Metabolism

- 1 E Gordon Young and F A H Rice (by invitation), *Dalhousie University, Halifax, Canada*
2-Keto-D gluconic acid in the polysaccharide of Irish moss
- 2 F B Seibert and Jane Atno and Mabel V Seibert (by invitation), *University of Pennsylvania, Philadelphia*
Changes in the serum proteins and carbohydrate in tuberculosis and methods of analysis
- 5 W Knowlton Hall, Katrine Rawls and V P Sydenstricker (introduced by A P Briggs), *University of Georgia School of Medicine, Augusta*
The excretion of certain urinary constituents in alkaptanuria
- 4 Alfred G Lisi and William M Hart (introduced by J Earl Thomas), *Jefferson Medical College, Philadelphia*
Analysis of lactic acid with a modification of the Conway microdiffusion unit

- 5 **J Raymond Klein and Ruth Hurwitz** (*by invitation*), *University of Illinois College of Medicine, Chicago*
Distribution of intravenously injected fructose and glucose between blood and brain
- 6 **Alfred E Koehler and Elsie Hill** (*by invitation*), *Santa Barbara Cottage Hospital and Sansum Clinic, Santa Barbara, California*
The effect of over-nutrition on ketosis
- 7 **D Rittenberg, Ernest Borek** (*by invitation*) and **Konrad Bloch**, *Columbia University*
Synthesis of cholesterol in liver slices
- 8 **DeWitt Stetten, Jr, and Babette V Klein** (*by invitation*), *Columbia University*
Effect of insulin level upon lipogenesis
- 9 **Ralph C Corley and Perrie D Somers** (*by invitation*), *Purdue University, Lafayette, Indiana*
Influence of insulin on consumption of oxygen by slices of liver in the presence of succinate and related substrates
- 10 **Winston H Price** (*by invitation*), **Milton W Slein** (*by invitation*), **Sidney P Colowick** and **Gerty T Cori**, *Washington University School of Medicine, St Louis*
Effect of adrenal cortex extract on the hexokinase reaction

BIOCHEMISTRY B

Tuesday, 9 00 a m

(See Bulletin Board for location)

Nitrogen Metabolism, Amino Acids

- 1 **Konrad Bloch and D Rittenberg**, *Columbia University, New York*
Acetylation of foreign amines by acetyl amino acids
- 2 **Kamel H Basinski** (*by invitation*) and **Robert R Sealock**, *University of Rochester*
Ascorbic acid and tyrosine metabolism
- 3 **Robert R Sealock and Tien Ho Lan** (*by invitation*), *Iowa State College, Ames, and University of Rochester*
Oxidation of 1-3,4-dihydroxyphenylalanine by normal and scorbutic kidney tissue
- 4 **Phyllis A Bott**, *Women's Medical College of Pennsylvania, Philadelphia*
A reinvestigation of the possible secretion of creatinine by the kidney tubules of the necturus
- 5 **S A Singal** (*by invitation*), **A P Briggs** and **V P Sydenstricker** and **Julia Littlejohn** (*by invitation*), *University of Georgia School of Medicine, Augusta*

- Effect of tryptophane on urinary excretion of nicotinic acid in rats
- 6 **Richard J Block**, *New York Medical College*
The separation of amino acids with the aid of ion exchangers
- 7 **Martin E Hanke**, *University of Chicago*
Precise estimation of lysine in the Van Slyke Neill manometric apparatus with a specific decarboxylase
- 8 **John A Nelson** (*by invitation*), **William D McFarlane** and **Marcel Boulet** (*by invitation*), *McGill University, Quebec, Canada*
A colorimetric method for the determination of lysine
- 9 **Anthony A Albanese, L Emmett Holt, Jr, Jane E Frankston** (*by invitation*) and **Virginia Irby** (*by invitation*), *New York University College of Medicine*
Estimation and characterization of bound amino N of normal human urine

BIOCHEMISTRY C

Tuesday, 9 00 a m

(See Bulletin Board for location)

Growth Factors and Vitamin Studies

- 1 **C A Cary and A M Hartman, L P Dryden, G D Likely** (*by invitation*), *U S Department of Agriculture, Washington, D C*
An unidentified factor essential for rat growth
- 2 **A M Hartman** (*introduced by C A Cary*), *U S Department of Agriculture, Washington, D C*
Occurrence in foods, of an unidentified factor essential for rat growth
- 3 **G M Briggs and R J Lillie** (*introduced by N R Ellis*), *University of Maryland, College Park*
Folic acid in the prevention of abnormal feather pigmentation of chicks fed purified diets
- 4 **Max Rubin and H R Bird** (*introduced by N R Ellis*), *Agricultural Research Center, Beltsville, Maryland*
Concentration and properties of a chick growth factor occurring in cow manure
- 5 **Joseph H Roe and Carl A Kuether, and Ruth G Zimler** (*by invitation*), *George Washington University, Washington, D C*
Studies on the distribution of ascorbic acid in blood
- 6 **Robert E Johnson**, *Harvard University, Boston, Mass*
Rate of urinary excretion of ascorbic acid, thiamine, riboflavin and N¹-methyl-nicotin-

amide and the effects of diuresis, alkalosis, acidosis and ingestion of food

- 7 M K Horwitt, O Kreisler (*by invitation*) and Ray D Williams, *Elgin State Hospital, University of Illinois College of Medicine, Chicago, Washington University, St Louis*
Factors affecting the levels of lactic and pyruvic acids in the blood
- 8 L Emmett Holt, Jr, Rosa Lee Nemir (*by invitation*), Katherine C Ketron (*by invitation*), Selma Synderman (*by invitation*), and Anthony A Albanese, *New York University*
The thiamine requirement of infants

BIOCHEMISTRY D

Tuesday, 9 00 a m

(See Bulletin Board for location)

Mineral Metabolism

- 1 W D Arms' strong, *University of Minnesota, Minneapolis*
Mechanism of skeletal disuse atrophy
- 2 D Harold Copp (*by invitation*) and David M Greenberg, *University of California Medical School, Berkeley*
A tracer study of iron metabolism with radioactive iron absorption, excretion, utilization and storage
- 5 Marlene Falkenheim (*by invitation*) and Harold C Hodge, *University of Rochester, School of Medicine and Dentistry, Rochester, New York*
Phosphate exchange in bone using radiophosphorus *in vitro*
- 4 S Granick (*introduced by L Michaelis*), *The Rockefeller Institute for Medical Research, New York*
Function of ferritin in regulating the absorption of iron by the gastrointestinal mucosa
- 5 A G Hogan and W O Regan (*by invitation*), *University of Missouri, Columbia*
Diet and calcium phosphate deposits in guinea pigs
- 6 C M McCay and J S Restarski, J G Bieri and Ross A Gortner, Jr (*by invitation*), *Natal Medical Research Institute, Bethesda, Maryland*
Effects of acid beverages containing fluoride on the teeth and bones of dogs
- 7 Wilbur R Tweedy and Max E Chilcote and Mary C Patras (*by invitation*), *Loyola University School of Medicine, Chicago, Illinois*
Distribution, retention, and excretion of radiophosphorus following thyroparathyroidectomy and the injection of parathyroid extract

BIOCHEMISTRY

Tuesday, 2 00 p m

BALLROOM

Symposium on Some Recent Trends in *Neurospora* Biochemistry

Herschel K Mitchell, *Chairman*

- 1 Edward L Tatum, *Yale University*
Introduction *Neurospora* as a biochemical tool
- 2 Francis J Ryan, *Columbia University*
The application of *Neurospora* to bioassay
- 3 Herschel K Mitchell and Mary B Houlahan, *Stanford University*
A preliminary report on the adenine mutants of *Neurospora*
- 4 William D McElroy, *Johns Hopkins University* and Herschel K Mitchell, *Stanford University*
Enzymatic studies on a temperature sensitive mutant of *Neurospora*
- 5 Sterling Emerson, *California Institute of Technology* and John E Cushing, *Johns Hopkins University*
Altered sulfonamide antagonisms in *Neurospora*

7 30 p m Business meeting

BIOCHEMISTRY A

Wednesday, 9 00 a m

(See Bulletin Board for location)

Carbon Metabolism (cld) and Respiratory Enzymes

- 1 Johanna M Lee (*by invitation*), William H Summerson and Vincent du Vigneaud, *Cornell University Medical College, New York*
Further studies on the rôle of biotin in mammalian tissue metabolism
- 2 John M Buchanan (*by invitation*), Warwick Sakami (*by invitation*), Samuel Gurin and Wright Wilson, *University of Pennsylvania, Philadelphia*
Intermediates of acetoacetate oxidation
- 3 E S Guzman Barron, Grant R Bartlett (*by invitation*), and George Kalnitsky (*by invitation*)
The oxidative pathway of pyruvate metabolism
- 4 David B Sprinson and Erwin Chargaff, *Columbia University*
The chemistry and biological significance of hydroxy keto acids

- 5 Severo Ochoa, *New York University College of Medicine*
Enzymatic formation of C_4 tricarboxylic acids by CO_2 fixation
- 6 M Blanchard (by invitation), D E Green, V Nocito-Carroll (by invitation) and S Ratner, *Columbia University, New York*
L-Hydroxy acid oxidase
- 7 H Glaser and S Granick (introduced by L Michaelis), *The Rockefeller Institute for Medical Research, New York*
Biological determination of protoporphyrin
- 8 Marian W Kies (introduced by A K Balls) *U S Department of Agriculture*
Effect of Hemin Proteins on Soybean Lipoxidase
- 9 Harry G Albaum, Alex B Novikoff, and Maurice Ogur (introduced by Elvin A Kabat), *Brooklyn College*
The relationship between cytochrome oxidase and succinic dehydrogenase in the developing chick embryo
- 10 Harry G Albaum (by invitation), Jay Tepperman (by invitation) and Oscar Bodansky, *Edgewood Arsenal, Maryland*
The in vivo inactivation of brain cytochrome oxidase and its effect on glycolysis and on high energy phosphorus reservoirs in brain
- 11 B L Horecker and Arthur Kornberg (introduced by Harry D Baernstein), *National Institute of Health, Bethesda, Maryland*
The cytochrome C-cyanide complex
- 6 H Fraenkel-Conrat, Beatrice Brandon (by invitation) and Harold S Olcott, *U S Department of Agriculture*
Chemical characterization and crystallization of formaldehyde derivatives of gramicidin
- 7 Gordon Alderton (by invitation), H L Fevold, and H D Lighbody, *U S Department of Agriculture*
Some properties of lysozyme
- 8 H L Fevold and Adele Lausten (by invitation) *U S Department of Agriculture*
Isolation of a new lipoprotein (lipovitellenin) from egg yolk
- 9 Lemuel D Wright and Helen R Skeggs (introduced by L Earle Arnow), *Sharp and Dohme, Inc, Glenolden, Pennsylvania*
A method for determining the affinity of avidin for analogs of biotin

BIOCHEMISTRY C

Wednesday, 9 00 a m

(See Bulletin Board for location)

Vitamins (ctd)

- 1 W O Caster (by invitation), Olaf Mickelsen and Ancel Keys, *University of Minnesota, Minneapolis*
Relation between the urinary excretion of thiamine and pyrimin (the pyrimidine-like component of thiamine)
- 2 E M Shantz (by invitation), N D Embree (by invitation), H C Hodge, and J H Wills, Jr (by invitation), *University of Rochester, New York*
Replacement of vitamin A_1 by vitamin A_2 in the retina of the rat
- 3 S W Clausen and A B McCoord and B L Goff (by invitation), *University of Rochester School of Medicine*
Comparison of the absorption of ester and alcohol vitamin A by human subjects
- 4 Elizabeth C Callison (by invitation) and Elsa Orent-Keiles, *U S Department of Agriculture, Beltsville, Maryland*
Effect of solvent upon utilization of beta-carotene for vitamin A storage
- 5 Elsa Orent-Keiles and Elizabeth C Callison (by invitation), *U S Department of Agriculture, Beltsville, Maryland*
Storage of vitamin A as influenced by composition of the diet
- 6 Albert E Sobel and Harold Werbin (by invitation), *Jewish Hospital of Brooklyn, N Y*
Activated glycerol dichlorohydrin a new colorimetric reagent for vitamin A
- 7 Albert E Sobel and Harold Werbin (by invitation), *Jewish Hospital of Brooklyn, N Y*
Estimation of vitamin A in fish liver oils by activated glycerol dichlorohydrin

BIOCHEMISTRY B

Wednesday, 9 00 a m

(See Bulletin Board for location)

Amino Acids (ctd), Proteins

- 1 Louis Berger (by invitation) and Philip A Shaffer, *Washington University School of Medicine, St Louis*
Kinetics of the iodination of tyrosine
- 2 Heinrich Waelsch and Blanche A Prescott (by invitation), *New York State Psychiatric Institute and Hospital*
Glutamic acid content of human blood serum
- 3 Ernest Borek (by invitation), Phyllis Sheiness (by invitation) and Heinrich Waelsch, *New York State Psychiatric Institute and Hospital*
Methionine sulfoxide a growth inhibiting analogue of glutamic acid
- 4 Arthur Kornberg (introduced by W H Sebrell), *National Institute of Health, Bethesda*
Amino acids in the production of granulocytes in rats
- 5 Choh Hao Li, *University of California, Berkeley*
Iodination of tyrosine groups in "regenerated" serum albumin

BIOCHEMISTRY D

Wednesday, 9 a m

(See Bulletin Board for location)

Biochemistry of Therapeutic and Toxic Substances

- 1 George H Hogeboom (by invitation) and Lyman C Craig, *The Rockefeller Institute for Medical Research, New York*
The use of the "counter-current distribution" technique for the isolation of biologically active principles
- 2 L O Kramptitz (by invitation) and C H Werkman, *Iowa State College, Ames*
On the mode of action of penicillin
- 3 Granvil C Kyker, Mildred McEwen, E McG Hedgpeth, and Violet Young (introduced by James C Andrews), *University of North Carolina, Chapel Hill*
Quinine, avitaminosis, and motility
- 4 Lyman C Craig and Elwood Titus, Harold Mighton, Calvin Golumbic and Malcolm Siegel (by invitation), *The Rockefeller Institute for Medical Research, New York*
Study of the metabolic products of several synthetic antimalarials in the human
- 5 J Logan Irvin and Elinor Moore Irvin (by invitation), *The Johns Hopkins University, School of Medicine, Baltimore*
Acid-base reactions of quinoline and acridine derivatives
- 6 B B Westfall (by invitation) and H P Morris, *National Cancer Institute, Bethesda, Maryland*
Studies on the metabolism of 2 acetylamino-fluorine in rats
- 7 W A Perlzweig, J W Huff (by invitation) and F Rosen (by invitation), *Duke University Medical School, Durham, N C*
The effect of CCl_4 poisoning on the fate of N^1 -methylnicotinamide in the rat
- 8 Eunice V Flock and Jesse L Bollman, *The Mayo Foundation, Rochester, Minnesota*
Phospholipid synthesis in damaged and regenerating liver

BIOCHEMISTRY

Wednesday, 2 00 p m

BALLROOM

Symposium on The Isotope Technique as Applied to Biochemistry

A Baird Hastings, Chairman

- 1 Allen Reid, *Columbia University*
The concentration and the measurement of the stable isotopes

- 2 M D Kamen, *Washington University*
The preparation and measurement of the radioactive isotopes with special reference to C^{11} , C^{14} , H^3 and H^{32}
- 3 D Shemin, *Columbia University*
The application of N^{15} to the study of the metabolism of nitrogenous compounds
- 4 D Rittenberg, *Columbia University*
The biochemical applications of deuterium
- 5 H G Wood, *University of Minnesota*
The biochemical application of the various carbon isotopes (C^{11} , C^{13} , and C^{14})

BIOCHEMISTRY

Thursday 11 a m

Business meeting

BIOCHEMISTRY A

Thursday, 2 00 p m

(See Bulletin Board for location)

Respiratory Enzymes (ctd) and other Enzymes

- 1 John Fuller Taylor, Arda Alden Green and Gerty T Cori, *Washington University School of Medicine, St Louis*
Crystalline aldolase and its identity with myogen A
- 2 Dean Burk and Arthur L Schade, Marie L Hesselbach, and Clara E Fischer (by invitation), *National Institute of Health, Bethesda, Maryland, and Overly Biochemical Research Foundation, New York*
Cobalt inhibition of tissue respiration, glycolysis, and growth
- 3 Zacharias Dische, *Columbia University, New York*
Regulation of phosphorylations in anaerobic glycolysis of red cells by its intermediary products
- 4 Haron O Singher and Nathan Millman (introduced by R A Woodbury), *Ortho Research Foundation, Lander, New Jersey*
The adenosinetriphosphatase activity of smooth muscle
- 5 P K Stumpf (by invitation) and D E Green, *Columbia University, New York*
d-Amino acid oxidase of *proteus morgani*
- 6 L F Leloir (by invitation) and D E Green, *Columbia University, New York*
Histamine Oxidase
- 7 Fritz Lipmann and Nathan O Kaplan (by invitation), *Massachusetts General Hospital, Boston*
Report on a coenzyme for acetylation
- 8 M Berman and D Nachmansohn (introduced by H T Clarke), *Columbia University, New York*

On the formation of acetylcholine by choline acetylase in the nerve axon

- 9 **Morris A Lipton** (*introduced by E S Gurman Barron*)

The mechanism of the enzymatic synthesis of acetylcholine

- 10 **Karl Meyer and Eleanor Hahnel** (*by invitation*), *Columbia University and Presbyterian Hospital, New York*

Lysozyme as a mucolytic enzyme

BIOCHEMISTRY B

Thursday, 2 00 p m

(See Bulletin Board for location)

Proteins (ctd)

- 1 **Charles E Carter** (*by invitation*) and **Jesse P Greenstein**, *National Institute of Health, Bethesda, Maryland*

Thymus nucleate and the heat coagulation of egg albumin

- 2 **Kurt G Stern and Sanford Davis** (*by invitation*), *Polytechnic Institute, Brooklyn, N Y*

Studies on thymus nucleohistone

- 3 **Erwin Chargaff**, *Columbia University, New York*

A nucleoprotein from avian tubercle bacilli

- 4 **David Shemin and D Rittenberg**, *Columbia University, New York*

Studies on the formation of heme and on the average life time of the human red blood cell

- 5 **David L Drabkin**, *University of Pennsylvania, Philadelphia*

The maintenance of active hemoglobin—a function of erythrocytes

- 6 **Paul B Hamilton** (*by invitation*) and **Lee E Farr**, *Rockefeller Institute for Medical Research, New York*

Hemoglobin solutions suitable for intravenous administration

- 7 **Lee E Farr and Alma Hiller**, *Rockefeller Institute for Medical Research, New York*

Preparation of dried hemoglobin without loss of activity

- 8 **O H Gaebler and Helen Duggan** (*by invitation*), *Henry Ford Hospital, Detroit, Michigan*

Improvements in determinations of carbon monoxide, bromsulphalein, and plasma dyes

- 9 **Aaron Bendich** (*by invitation*) and **Erwin Chargaff**, *Columbia University, New York*

The isolation and characterization of two antigenic fractions of proteus OX-19

- 10 **Emil L Smith** (*introduced by O Wintersteiner*) *E R Squibb & Sons, New Brunswick, N J*

The immune proteins of the cow

BIOCHEMISTRY C

Thursday, 2 00 p m

(See Bulletin Board for location)

Steroids

- 1 **M Spiegel-Adolph and G C Henny** (*by invitation*), *Temple University School of Medicine, Philadelphia*

X-ray diffraction studies on gallstones

- 2 **Alfred C Koehler and Elsie Hill** (*by invitation*), *The Santa Barbara Cottage Hospital and The Sansum Clinic, Santa Barbara, California*

The rate of the Liebermann-Burchard cholesterol color reaction

- 3 **Wright Langham** (*by invitation*) and **R G Gustavson**, *University of Colorado*

Effect of level of thyroid activity on response of ovariectomized rats to estrone

- 4 **Eleanor H Venning and J S L Browne** (*by invitation*), *Royal Victoria Hospital, Montreal, Canada*

Excretion of urinary corticoid hormones by man in health and disease

- 5 **Harold L Mason and Edward J Kepler** (*by invitation*), *Mayo Clinic, Rochester, Minnesota*

The metabolism of dehydroisoandrosterone

- 6 **H Hirschmann** (*introduced by Ralph I Dorfman*), *Western Reserve University and the Lakeside Hospital, Cleveland, Ohio*

Studies in steroid excretion

BIOCHEMISTRY D

Thursday, 2 00 p m

BALLROOM

Joint Session with the Pharmacological Society Disopropyl fluorophosphate

- 1 **Oscar Bodansky and Abraham Mazur**, *Chemical Warfare Service, Edgewood Arsenal, Maryland*

The mechanism of in vitro and in vivo inhibition of cholinesterase activity by disopropyl fluorophosphate

- 2 **Abraham Mazur**, *Chemical Warfare Service, Edgewood Arsenal, Maryland*

An enzyme in the animal organism capable of hydrolyzing disopropyl fluorophosphate

- 3 **George B Koelle** (*by invitation*) and **Alfred Gilman**, *Chemical Warfare Service, Edgewood Arsenal, Maryland*

The chronic toxicity of disopropyl fluorophosphate (DFP) in dogs, monkeys and rats

- 4 Walter F Riker and William C Wescoe (introduced by McKeen Cattell), *Cornell University Medical College, New York*
Comparative studies on the nicotinic action of diisopropyl fluorophosphate (DFP)
- 5 Rudolph Koster (introduced by McKeen Cattell), *Cornell University Medical College, New York*
The synergistic and antagonistic effects of diisopropyl fluorophosphate (DFP) and phystostigmine in the cat
- 6 M A Rothenberg and D Nachmansohn (introduced by H T Clark), *Columbia University, New York*
On the permeability of the nerve axon to diisopropyl fluorophosphate (DFP)
- 7 Frederick Crescitelli (by invitation), George B Koelle (by invitation) and Alfred Gilman, *Chemical Warfare Service, Edgewood Arsenal, Maryland*
Nerve conduction in absence of cholinesterase activity induced by diisopropyl fluorophosphate (DFP)
- 8 A McGehee Harvey, Benjamin F Jones, Samuel Talbot and David Grob (introduced by Oscar Bodansky), *The Johns Hopkins Medical School, Baltimore, Maryland*
The effect of diisopropyl fluorophosphate (DFP) on neuromuscular transmission in normal individuals and in patients with myasthenia gravis
- 9 J Todd (by invitation), J H Comroe, Jr, George Gammon (by invitation), George Koelle (by invitation) and Alfred Gilman, *University of Pennsylvania Medical School, Philadelphia, and Chemical Warfare Service Edgewood Arsenal, Maryland*
The effect of diisopropyl fluorophosphate (DFP) on normal men and patients with myasthenia gravis
- 10 I H Leopold (by invitation) and J H Comroe, Jr, *University of Pennsylvania Medical School, Philadelphia*
The effect of diisopropyl fluorophosphate (DFP) on the normal and glaucomatous eye
- 3 Michael Laskowski, *Marquette University School of Medicine, Milwaukee*
Partial purification of thymonucleodepolymerase
- 4 Otto Schales, Virginia Mims (by invitation) and Selma S Schales (by invitation), *Alton Ochsner Medical Foundation, New Orleans*
Glutamic acid decarboxylase of higher plants
- 5 Hans Lineweaver and Eugene F Jansen, L R MacDonnell and Josie Jang (by invitation), *U S Department of Agriculture*
The specificity of pectinesterase of higher plants
- 6 Armand J Quick, *Marquette University School of Medicine, Milwaukee*
Influence of decalcification on the determination of prothrombin
- 7 Lowell O Randall, *The Wellcome Research Laboratories, Tuckahoe, N Y*
Reaction of thiol compounds with hydrogen peroxide and peroxidase
- 8 P K Stumpf (by invitation) and D E Green, *Columbia University, New York*
On the mode of action of chlorinating compounds
- 9 Donald E Bowman, *Indiana University School of Medicine, Indianapolis*
Influence of iodination of tryptic activity

BIOCHEMISTRY B

Friday, 9 00 a m

(See Bulletin Board for location)

Studies on Growth and Protein Metabolism

- 1 Choh Hao Li, *University of California, Berkeley*
Sulfur amino acids in growth and adrenocorticotrophic hormones
- 2 Arthur J Mueller (by invitation), Warren M Cox, Jr and Dorothy Sloat (by invitation), *Mead Johnson & Company*
Supplementation of casein and a casein hydrolysate with cystine and methionine
- 3 Douglas V Frost, Jean Heinsen, and Robert T Olsen (introduced by D W MacCorquodale), *Abbott Laboratories, North Chicago, Illinois*
The use of high levels of partial acid hydrolysates of proteins intravenously in hypoproteinemic dogs
- 4 Anthony A Albanese and Virginia Irby and Jane E Frankston (by invitation), *New York University College of Medicine*
Effect of carbohydrate feeding on the urinary output of amino acid and other metabolites in man
- 5 Herbert C Tidwell (by invitation) and C R Treadwell, *Southwestern Medical College, Dallas, Texas*

BIOCHEMISTRY A

Friday, 9 00 a m

(See Bulletin Board for location)

Enzymes continued

- 1 Irwin W Sizer, *Massachusetts Institute of Technology, Cambridge*
Action of tyrosinase on proteins
- 2 Sidney P Colowick and Winston H Price (by invitation), *Washington University, School of Medicine, St Louis*
Enzymatic formation of guanine by a reversible phosphorolytic cleavage of ribonucleic acid

Relation of fasting ketosis to the protein of the preceding diet

- 6 Barnett Sure, *University of Arkansas, Fayetteville*

Dietary requirements for fertility and lactation XXXIII Dried yeasts as sources of proteins and vitamin B complex for growth, reproduction and lactation

- 7 Charles F Kade and Jean Houston (*by invitation*) and Melville Sahyun, *Fredrick Stearns & Company Division, Sterling Drug, Inc., Detroit*

The maintenance of nitrogen balance on low nitrogen and low caloric intakes

BIOCHEMISTRY C

Friday, 9 00 a m

(See Bulletin Board for location)

Lipids

- 1 Colin C Lucas (*by invitation*), C H Best, Jessie H Ridout (*by invitation*) and Jean M Patterson (*by invitation*), *University of Toronto*

The lipotropic factors

- 2 Jordi Folch, *Rockefeller Institute, New York, and Harvard Medical School, Waverley, Mass*

Isolation of brain diphosphoinositide, a new phosphatide containing inositol meta diphosphate as a constituent

- 3 Warren M Sperry and Florence C Brand (*by invitation*), *New York State Psychiatric Institute and Hospital*

The hydrolysis of sphingomyelin

- 4 Mary C Panghorn, *New York State Department of Health, Albany, N Y*

A study of the composition of cardiolipin

- 5 G Schmidt, J Benotti (*by invitation*) and S J Thannhauser, *J Pratt Diagnostic Hospital and Tufts Medical School, Boston*

A method for the microdetermination of sphingomyelin in tissues

- 6 Elizabeth Pinkerton, E L MacQuiddy and Hartmann Goetze (*by invitation*) and Fred W Oberst, *University of Nebraska, Omaha, and Wm S Merrell Company, Cincinnati, Ohio*

Fate of sodium ricinoleate after oral administration to white rats

BIOCHEMISTRY D

Friday, 9 a m

(See Bulletin Board for location)

Biochemistry of Toxic Substances (ctd)

- 1 Herbert P Sarett and Bernard J Jandorf (*introduced by Oscar Bodansky*), *Chemical*

Warfare Service, Edgewood Arsenal, Maryland

Effects of chronic intoxication of rats with DDI on lipids and other constituents of liver

- 2 R G Sinclair, G Hale, and D Fairbairn (*by invitation*), *Queen's University, Kingston, Canada*

Lipid mustard compounds

- 3 Alfred Chanutin and Stephan Ludewig, *University of Virginia*

Effect on adrenal constituents of injury to rats

- 4 Irland C Gjessing (*by invitation*) and Alfred Chanutin, *University of Virginia*

Electrophoretic changes in the serum protein patterns of dogs subjected to various types of injury

- 5 Stephan Ludewig, Irland G Gjessing (*by invitation*) and Alfred Chanutin, *University of Virginia*

Protein fractionation studies on the sera of control and injured dogs

BIOCHEMISTRY

Friday, 2 00 p m

BALLROOM

Symposium on Biochemistry of Malarial Parasites and the Mode of Action of Antimalarial Drugs

W M Clark, *Chairman*

- 1 K C Blanchard (*by invitation*)
A survey of the malarial problem
- 2 E A Evans, *University of Chicago*
Enzyme systems operating within the malarial parasite
- 3 E G Ball, *Harvard Medical School, Boston*
Chemical and nutritional observations on malarial parasites grown *in vitro*
- 4 L Hellerman, *Johns Hopkins University, Baltimore*
Metabolism of cell-free malarial parasites, with respect to the action of certain antimalarial agents
- 5 W B Wendel, *University of Tennessee, Memphis*
The influence of naphthoquinones upon the respiratory and carbohydrate metabolism of malarial parasites

(PAPERS READ BY TITLE)

BIOCHEMISTRY

- 1 James C Andrews and W E Cornatzer (*by invitation*), *University of North Carolina*
Metabolism of cinchonine in dogs and man
- 2 W D Armstrong, *University of Minnesota*
Skeletal atrophy from disuse

- 3 A K Balls and Bernard Axelrod and Marian W Kies (*by invitation*), *U S Department of Agriculture*
Activator for soy bean lipovdase
- 4 Bernard B Brodie, Sidney Udenfriend (*by invitation*), John E Baer (*by invitation*), *New York University*
A scheme for the analysis of basic organic compounds in biological tissues, 1 Isolation prior to estimation
- 5 Bernard B Brodie, Sidney Udenfriend (*by invitation*), Wesley Dill (*by invitation*), *New York University*
A scheme for the analysis of basic organic compounds in biological tissues 2 Estimation of fluorescent compounds
- 6 Bernard B Brodie, Sidney Udenfriend (*by invitation*), Wesley Dill (*by invitation*), and Theodore Chenkin (*by invitation*), *New York University*
A scheme for the analysis of basic organic compounds in biological tissues 3 Estimation by conversion to fluorescent compounds
- 7 Bernard B Brodie, Sidney Udenfriend (*by invitation*), and John V Taggart (*by invitation*), *New York University*
A scheme for the analysis of basic organic compounds in biological tissues 4 The estimation of compounds by coupling with diazonium salts
- 8 Bernard B Brodie, Sidney Udenfriend (*by invitation*) and Wesley Dill (*by invitation*), *New York University*
A scheme for the analysis of basic organic compounds in biological tissues 5 Estimation of compounds by salt formation with methyl orange
- 9 Charles E Carter (*by invitation*), and Jesse P Greenstein, *National Institute of Health*
Thymus nucleate and the heat coagulation of aqueous tissue extracts
- 10 Philip P Cohen and Mika Hayano (*by invitation*), *University of Wisconsin*
The rôle of amides in urea synthesis
- 11 A C Corcoran and Irvine H Page with the assistance of R H Harris, *Cleveland Clinic Foundation*
A method for the determination of mannitol in blood and urine
- 12 W J Dann and Jesse W Huff (*by invitation*), *Duke University*
Metabolism of excess of nicotinamide by the chicken
- 13 Zacharias Dische, *Columbia University*
A characteristic and sensitive colour reaction of SH compounds
- 14 Robert S Gordon, Jr (*by invitation*) and John D Ferry, *Harvard University Medical School*
Studies of the melting points of gelatin gels
- 15 E Hay, P Seguin (*by invitation*) M Larivière (*by invitation*) and H Jensen, *University of Montreal*
The renotropic effect of the anterior pituitary
- 16 Edward S Josephson, *U S Public Health Service (by invitation)*, Sidney Udenfriend (*by invitation*), and Bernard B Brodie, *New York University*
A scheme for the analysis of basic organic compounds in biological tissues 6 Ultraviolet spectrophotometry
- 17 Barbara Kennedy (*by invitation*) and Ruth Okey, *University of California*
Effect of splenectomy on the anemia of cholesterol fed guinea pigs
- 18 Agnes Fav Morgan, Helen E Axelrod and Mary Groody (*by invitation*), *University of California*
Effects of a single massive dose of vitamin D₂ on young dogs
- 19 Paul K Smith, Lt Col, Jane R Bayliss, S Orgozalek and Margaret M McClure, *AAF School of Aviation Medicine, Randolph Field, Texas*
Metabolism of large doses of para-aminobenzoic acid
- 20 M Spiegel-Adolph and H T Wycis and E A Spiegel (*by invitation*), *Temple Medical School*
Enzymatic action of cerebrospinal fluid following concussion
- 21 Henry Longstreet Taylor, Glenn Fischer (*by invitation*), Samuel M Wells (*by invitation*) and Ancel Keys, *University of Minnesota*
The effect of experimental malaria on the electrophoretic pattern of the serum proteins of normal young men

PHARMACOLOGY A

Tuesday, 9 00 a m

Room 9

Analgesics, Anesthetics

- 1 Anna J Eisenman, *Research Department, U S Public Health Service Hospital*
The effect of morphine on the oxygen saturation of arterial blood (Biochem)
- 2 Abraham Wikler, *U S P H S Research Department, U S Public Health Service Hospital*
Reactions of chronic totally decorticated dogs during a cycle of morphine addiction
- 3 Ewart A Swinyard (*by invitation*), James E P Toman, and Louis S Goodman, *University of Utah School of Medicine*
The effects of body water and electrolyte shifts on experimental convulsions

- 4 **Louis S Goodman, Ewart A Swinyard** (*by invitation*), and **James E P Toman**, *University of Utah School of Medicine*

Further studies on the anticonvulsant properties of tridione (3,5,5-trimethylloxazolidinedione)

- 5 **R W Whitehead, L W Roth** (*by invitation*), and **W B Draper**, *University of Colorado*

Antidotal action of metrazol against pentothal sodium overdose

- 6 **Byron B Clark and Miriam Spitalny** (*by invitation*), *Albany Medical College, Union University*

Prothrombinopenic activity of the salicylates and pharmacologically related drugs

- 7 **Paul K Smith, Helen L Gleason, Charles B Stoll, and S Orgorzalek**, *Randolph Field AAF School of Aviation Medicine*

Studies on the pharmacology of salicylates

- 8 **Charles M Gruber and Goldie Freedman Keyser** (*by invitation*), *Jefferson Medical College*

The response of the isolated frog heart to different barbiturates

- 9 **E Leong Way**, (*introduced by George B Roth*), *The George Washington University School of Medicine*

One way isompeccaine-barbiturate antagonism

- 10 **Edwin J Fellows**, *Temple University School of Medicine*

The analgesic action of the racemates of I-amino-1-phthalidylpropane hydrochloride

- 11 **E Ross Hart**, *Jefferson Medical College*

The analgetic potency and acute toxicity of salicylamide and certain of its derivatives as compared with established analgetic-antipyretic drugs

- 12 **Charles C Scott and K K Chen**, *Lilly Research Laboratories*

The action of 1,1-diphenyl-1-(dimethylaminoisopropyl)-butanone-2, a potent analgesic agent

- 13 **Albert R Latven** (*by invitation*), **Walter A Freyburger** (*by invitation*), and **Karl H Beyer**, *The Medical Research Division, Sharp and Dohme, Inc*

The relationship of structure to activity and toxicity of a series of local anesthetic agents

- 14 **H R Hulpieu and V V Cole**, *Indiana University School of Medicine*

Potentiation of the depressant action of alcohol by adrenalin

- 15 **John C Krantz, Jr**, *University of Maryland School of Medicine*

The anesthetic properties of n-propyl methyl ether

PHARMACOLOGY B

Tuesday, 9 00 a m

COMMITTEE ROOM 1

- 1 **Kathleen G W Seymour** (*by invitation*) and **Lidon M Boyd**, *Queen's University*

The antipyretic action of camphor

- 2 **Lloyd W Hazleton and Rebecca C Hellerman** (*by invitation*), *The George Washington University, The Kalusowski Memorial Research Laboratory*

Studies on the pharmacology of cholic acid

- 3 **Anthony M Ambrose and Floyd DeEds**, *Bureau of Agricultural and Industrial Chemistry U S Department of Agriculture*

Pharmacological properties of citrinin

- 4 **Hamilton H Anderson, Victor P Bond, and Benedict E Abreu**, *University of California Medical School*

Pharmacologic properties of p-carbamidophenylarsenous oxide

- 5 **R K Richards**, *Abbott Laboratories*

Inhibition of procaine induced convulsions by its split products (Physiol)

- 6 **Guy M Everett** (*introduced by R K Richards*), *Abbott Laboratories*

Anticonvulsant action of drugs against metrazol and anti-epileptic activity (Physiol)

- 7 **C J Campbell** (*by invitation*), **J P Maes**, and **R M Barrett** (*by invitation*), *Dartmouth Medical School*

Sodium succinate as an analeptic in man (Physiol)

- 8 **R A Waud and Ruth Horner** (*by invitation*), *University of Western Ontario Medical School*

The treatment of pulmonary edema with suction and certain drugs

- 9 **Charles R Thompson** (*by invitation*) and **Harold W Werner**, *Research Laboratories, The Wm S Merrell Co*

Studies on the fate of tri-p-amyl chloroethylene and hexestrol

- 10 **W Glenn Moss** (*by invitation*) and **C C Pfeiffer**, *University of Illinois College of Medicine*

Quantitative studies on intradermal wheals I Pressure required to produce cutaneous wheals

- 11 **C C Pfeiffer**, *University of Illinois College of Medicine*

Quantitative studies on intradermal wheals II The use of a skin plethysmograph to study changes in the volume of cutaneous wheals

- 12 **R W Dingwall** (*by invitation*) and **E M Boyd**, *Queen's University*

The absorption, distribution and elimination of different pharmaceutical forms of sulphadiazine

PHARMACOLOGY C

Tuesday, 9 00 a m

COMMITTEE ROOM 2

Papers Transferred from Physiology

- 1 J H Bannon, Jr, D J W Escher, and M Bevelander (*introduced by Homer W Smith, New York University College of Medicine*)
The effect of the continuous administration of p aminopropiophenone on the blood in man (*Physiol*)
- 2 T C Barnes, Hahnemann Medical College and Hospital of Philadelphia
The effect of healing agents on the wound potential of human skin (*Physiol*)
- 3 E C del Pozo and G Anguiano L (*by invitation*), Instituto Politécnico Nacional, Mexico
Physiological actions of scorpion venom (*Physiol*)
- 4 A M Lands, Eleanor Rickards (*by invitation*), and V Loraine Nash (*by invitation*), Frederick Stearns and Co
Pharmacology of some vaso-depressor compounds (*Physiol*)
- 5 John R Lewis (*introduced by A M Lands, Frederick Stearns and Co*)
Potentiating and pressor action of some N-substituted hexylamines (*Physiol*)
- 6 Tsan-wen Li (*by invitation*) and Smith Freeman, Northwestern University Medical School
The effect of methionine on the growth of protein deficient rats exposed to benzene (*Physiol*)
- 7 David I Macht, Department of Pharmacology Laboratories of Sinai Hospital
Comparative toxicity of penicillin for animals and plants (*Physiol*)
- 8 A W Martin, Helen M Kipple (*by invitation*), J M Dille (*by invitation*), and Bernice G Harris (*by invitation*), University of Washington
Spinal and peripheral synaptic susceptibility to nembutal (sodium pentobarbital) as shown by vesicular responses (*Physiol*)
- 9 George Masson, McGill University
Effects of proteins on the resistance to anesthesia produced by barbiturates (*Physiol*)
- 10 H M Maling (*by invitation*) and G H Acheson, Harvard Medical School
Righting activity in spinal and decerebrate cats after d amphetamine (*Physiol*)
- 11 Willie W Smith, Industrial Hygiene Research Laboratory, National Institute of Health
The protective action of cystine and methionine in rats exposed to methyl chloride (*Physiol*)
- 12 C V Winder, C C Pfeiffer (*by invitation*), and G L Maisson, Research Department,

Parke, Davis and Co and Department of Pharmacology, Wayne University

The nociceptive contraction of the musculus cutaneous maximus in the guinea pig as elicited by radiant thermal skin stimulation, temporal and spatial summation and susceptibility to centrally acting analgetic drugs (*Physiol*)

PHARMACOLOGY A

Tuesday, 2 00 p m

Room 9

Parasympathetic and Related Drugs

- 1 Donald Slaughter, Southwestern Medical College
The modifying action of neostigmine on pain threshold responses to various opiates
- 2 Benedict E Abreu, Robert J Tufts, and Marjorie E Coutolenc, University of California Medical School
Central nervous system effects of anticholinergic agents
- 3 A Earl Vivino (*by invitation*) and Theodore Koppányi, Georgetown University School of Medicine
The interaction between neostigmine and epinephrine and the dimethylpiperidines
- 4 Theodore Koppányi and A Earl Vivino (*by invitation*), Georgetown University School of Medicine
Dimethylpiperidines as primary ganglionic depressants
- 5 M Shirley Lapp (*by invitation*) and E M Boyd, Queen's University
On the expectorant action of cholinergic drugs
- 6 M A Root (*introduced by O Krayner*), Harvard Medical School
Dose and intensity of action and elimination of prostigmine
- 7 Walter F Riker (*by invitation*), W Clarke Wescoe (*by invitation*), McKeen Cattell, and Ephraim Shorr, Cornell University Medical College and The New York Hospital
The mechanism of action of prostigmine
- 8 Carroll A Handley, Baylor University College of Medicine
The pharmacologic action of some derivatives of benzylcholine
- 9 Frederick K Bell (*by invitation*) and C Jelleff Carr, University of Maryland School of Medicine
The pharmacology of a new series of choline salts
- 10 Norman W Karr (*introduced by Benedict E Abreu*), University of California Medical School
A comparative study of substituted phenolic urethanes

- 11 R W Brauer and M A Root (*introduced by* O Krayser), *Harvard Medical School*
Liver injury and its influence upon the acetylcholine splitting activity of rat and dog

PHARMACOLOGY B

Tuesday, 2 00 p m

COMMITTEE ROOM 1

Joint Session, Biometrics Section, American Statistical Association, and The Pharmacological Society

- 1 M G Allmark, W M Bachinski (*by invitation*), and C A Morrell, *Laboratory of Hygiene, Department of National Health and Welfare, Canada*

The application of a graded type of response technique for the bio assay of pituitary extract (posterior lobe)

- 2 W Ray Bryan (*by invitation*), *National Cancer Institute, National Institute of Health, U S Public Health Service*

Use of the latent period in studies on the agent of chicken tumor I

- 3 C I Bliss and B L Bartels (*by invitation*), *Yale University and Connecticut Agricultural Experiment Station*

The determination of the most efficient response for measuring drug potency

- 4 E M Jellinek (*by invitation*), *Yale University*
Rôle of the placebo in tests for drug discrimination

- 5 Edwin J de Beer, *The Wellcome Research Laboratories*

A statistical examination of the sources of error in the assay of mydriatic drugs by means of the rabbit's pupil

- 6 L I Pugsley, *Laboratory of Hygiene, Department of National Health and Welfare, Canada*
Study of the variables affecting the precision of the assay of estrogens

PHARMACOLOGY C

Tuesday, 2 00 p m

COMMITTEE ROOM 2

Drug Toxicity, DDT, etc

- 1 Geoffrey Woodard and Ruth R Ofner (*introduced by* Bert J Vos, Jr), *Food and Drug Administration, Federal Security Agency*

Accumulation of DDT in the fat of rats in relation to dietary level and length of feeding

- 2 W F Von Oettingen and N E Sharpless (*by invitation*), *Industrial Hygiene Research Laboratory, National Institute of Health*

The relation between the chemical structure of DDT and its toxicity with oral administration to mice

- 3 M I Smith, H Bauer (*by invitation*), E F Stohlman (*by invitation*), and R D Lallie, *Division of Physiology and the Pathology Laboratory, National Institute of Health*

The pharmacologic action and metabolism of a series of compounds chemically related to DDT

- 4 J H Welsh and H T Gordon (*by invitation*), *Harvard University*

The mode of action of DDT (*Physiol*)

- 5 Bernard P McNamara (*by invitation*), Richard J Bing, and Francis (*by invitation*), *Chemical Warfare Service, Edgewood Arsenal*

- 6 Frederick S Philips (*by invitation*), Alfred Gilman, and Frederick Crescitelli (*by invitation*), *Chemical Warfare Service, Edgewood Arsenal*

The sensitization of the myocardium to sympathetic stimulation during acute DDT intoxication in mammals (*Physiol*)

- 7 K P Du Bois (*introduced by* E M K Geiling), *University of Chicago Toxicity Laboratory*

Biochemical studies on the toxicology of alpha-naphthylthiourea (ANTU)

- 8 Maynard B Chenoweth and Alfred Gilman, *Chemical Warfare Service, Edgewood Arsenal*
Pharmacology of fluoracetate

- 9 J L Whittenberger (*by invitation*), J Wexler (*by invitation*), S Himmelfarb (*by invitation*), and P R Dumke, *Chemical Warfare Service, Edgewood Arsenal*

The effect of methemoglobinemia on the respiratory stimulation by cyanide in man

- 10 Jack Wexler (*by invitation*), J L Whittenberger (*by invitation*), and P R Dumke, *Chemical Warfare Service, Edgewood Arsenal*

The effect of cyanide on the electrocardiogram of man

- 11 K K Vining, Jr, J L Whittenberger, A C Wollack (*introduced by* P R Dumke), *Chemical Warfare Service, Edgewood Arsenal*

A comparison of the effect of 7% carbon dioxide with 93% oxygen, and pure oxygen, on goats and dogs, acutely asphyxiated with carbon monoxide

- 12 Bernard J Jandorf (*by invitation*) and Oscar Bodansky, *Chemical Warfare Service, Edgewood Arsenal*

Rôle of methemoglobinemia in protection against and treatment of inhalation poisoning by HCN and CNCl

- 13 A J Dziemian (*introduced by* Paul Dumke), *Chemical Warfare Service, Edgewood Arsenal*

The effects of body-gassing with mustard vapor on the carbohydrate metabolism of dogs

PHARMACOLOGICAL SOCIETY BUSINESS MEETING

Tuesday, 7 30 p m

Room 9

PHARMACOLOGY

Wednesday, 9 00 a m

BALLROOM

Symposium on Advances in Pharmacology Resulting from War Research

A N RICHARDS, *Chairman*

- 1 Alfred Gilman, *Pharmacology Section, Medical Division, Chemical Warfare Service, Edgewood Arsenal*

Therapeutic applications of chemical warfare agents

- 2 Frederick S Philips, *Pharmacology Section, Medical Division, Chemical Warfare Service, Edgewood Arsenal*

Insecticides and rodenticides

- 3 E K Marshall, *Department of Pharmacology, Johns Hopkins University*

Malarial chemotherapy, 1941-1945

- 4 Hans Mohr, *Merck Institute for Therapeutic Research*

Bacterial chemotherapy

Professors August Krogh and Corneille Heymans will attend and participate in the discussion

PHARMACOLOGY A

Wednesday, 2 00 p m

Room 9

Chemotherapy and Pharmacology of Malaria

- 1 Robert W Berliner (by invitation), John V Taggart (by invitation), Charles G Zubrod (by invitation), William J Welch (by invitation), David P Earle, Jr (by invitation), and James A Shannon, *Research Service, Third Medical Division, Goldwater Memorial Hospital, and the Department of Medicine, New York University College of Medicine*

Cinchona alkaloids 1 Appraisal of suppressive antimalarial activity

- 2 Charles G Zubrod (by invitation), Robert W Berliner (by invitation), John V Taggart (by invitation), William J Welch (by invitation), David P Earle, Jr (by invitation), and James A Shannon, *Research Service, Third Medical Division, Goldwater Memorial Hospital, and the Department of Medicine, New York University College of Medicine*

Cinchona alkaloids 2 Comparative suppressive antimalarial activity

- 3 John V Taggart (by invitation), Robert W Berliner (by invitation), Charles G Zubrod (by invitation), William J Welch (by invitation), David P Earle, Jr (by invitation), and James A Shannon, *Research Service, Third Medical Division, Goldwater Memorial Hospital, and the Department of Medicine, New York University College of Medicine*

Cinchona alkaloids 3 Physiological disposition in man

- 4 Bernard B Brodie, John E Baer (by invitation), *Research Service, Third Medical Division, Goldwater Memorial Hospital, and the Department of Medicine, New York University College of Medicine, and Lyman C Craig, Rockefeller Institute for Medical Research*

Cinchona alkaloids 4 Metabolic products in human urine

- 5 David P Earle, Jr (introduced by James A Shannon), *Research Service, Third Medical Division, Goldwater Memorial Hospital, and the Department of Medicine, New York University College of Medicine*

Cinchona alkaloids 5 Physiological disposition of cinchonine metabolic products in man

- 6 William J Welch (by invitation), John V Taggart (by invitation), Robert W Berliner (by invitation), Charles G Zubrod (by invitation), David P Earle, Jr (by invitation), and James A Shannon, *Research Service, Third Medical Division, Goldwater Memorial Hospital, and the Department of Medicine, New York University College of Medicine*

Cinchona alkaloids 6 Suppressive antimalarial activity of cinchonine carbostyryl

- 7 W Eugene Knox (introduced by James A Shannon), *Research Service, Third Medical Division, Goldwater Memorial Hospital, and the Department of Medicine, New York University College of Medicine*

Cinchona alkaloids 7 The nature of the quinone oxidizing enzyme of liver

- 8 William D Blake (by invitation), Charles G Zubrod (by invitation), and Morris Rosenfeld, *Research Service, Third Medical Division, Goldwater Memorial Hospital, and the Department of Medicine, New York University College of Medicine*

Methemalbuminemia during combined therapy with pamaquine and quinine

- 9 Joseph W Jailer (by invitation), Charles G Zubrod (by invitation), Morris Rosenfeld, and James A Shannon, *Research Service, Third Medical Division, Goldwater Memorial Hospital, and the Department of Medicine, New York University College of Medicine*

Influence of altered acid base balance and anoxia upon the physiological disposition of certain antimalarial drugs

- 10 Thomas J Kennedy, Jr, (*by invitation*), Charles G Zubrod (*by invitation*), Frederick S Bigelow (*by invitation*), Robert W Berliner (*by invitation*), and James A Shannon, *Research Service, Third Medical Division, Goldwater Memorial Hospital, and the Department of Medicine, New York University College of Medicine*

A mechanism of drug "potentiation" Pamaquin metabolism as influenced by quinaerine

PHARMACOLOGY B

Wednesday, 2 00 p m

COMMITTEE ROOM 1

Drug Toxicity

- 1 Paul N Harris, K G Wakim, and K K Chen, *Lilly Research Laboratories and Indiana University Medical Center*
Effects of senecionine on the hamster and monkey
- 2 W A McOmie (*introduced by* Hamilton H Anderson), *University of California Medical School*
Certain aspects of the toxicity of diallyl phthalate
- 3 O Garth Fitzhugh, *Food and Drug Administration, Federal Security Agency*
Production of cataracts in rats with beta tetralol
- 4 John H Draize, Elsie Alvarez (*by invitation*), and Marie F Whitesell (*by invitation*), *Food and Drug Administration, Federal Security Agency*
Toxicity and primary irritation of some chemical compounds following oral administration and skin application
- 5 Alfred Gellhorn (*by invitation*) and H B van Dyke, *Department of Pharmacology, College of Physicians and Surgeons*
The tissue distribution and the excretion of antimony after administration of trivalent and quinquevalent antimomials
- 6 E P Laug and E A Vos, E J Umberger and F M Kunze (*by invitation*), *Food and Drug Administration, Federal Security Agency*
Percutaneous penetration of mercury in the rat (*Biochem*)
- 7 S Anderson Peoples, *Baylor University College of Medicine*
The effect of phloridzin on the renal excretion of mercury
- 8 Lloyd D Seager and Gina Castlenuovo (*by invitation*), *Woman's Medical College of Pennsylvania*
The acute and chronic toxicity of stilbamidine
- 9 R P Walton and C B Preacher (*by invitation*), *Medical College of South Carolina*
Toxicity of methylamino-iso-octene (octin)

- 10 Donald Mathieson (*by invitation*), Harry W Hays (*by invitation*), Dorothy Chess (*by invitation*), Anne Cameron (*by invitation*), and Fredrick F Yonkman, *Ciba Pharmaceutical Products, Inc*

Acute and chronic toxicity studies of pyri-benzamine hydrochloride (N'-pyridyl-N'-benzyl-N-dimethylethylenediamine HCl)

- 11 Harry Eagle, Harold J Magnuson, and Ralph Fleischman (*introduced by* E K Marshall), *Veneral Disease Research Laboratory of the U S Public Health Service, Johns Hopkins Hospital*

2,3 dithiolpropanol ("Bsl") as a specific detoxifying agent for arsenic

- 12 James L Morrison, *Emory University School of Medicine*

Toxicity of certain halogenated aliphatic acids for mice

- 13 H B Haag, J H Weatherby, Doris Fordham, and P S Larson, *Medical College of Virginia*
The effect on rats of daily-life span exposure to cigaret smoke

DISCUSSION ON THE TEACHING OF PHARMACOLOGY

Benedict E Abreu, *Chairman*

Wednesday, 8 00 p m

Room 9

PHARMACOLOGY A

Thursday, 9 00 a m

Room 9

Antiseptics and Chemotherapy

- 1 Andres Goth (*introduced by* Donald Slaughter), *Southwestern Medical College*
The effect of cobalt on the antitubercular activity of aspergillic acid
- 2 E L McCawley, B A Rubin, and N J Giacomino (*by invitation*), *Yale University School of Medicine*
A preliminary survey of certain lactone antibiotics
- 3 Gordon K Moe and M H Seevers, *University of Michigan*
Central impairment of sympathetic reflexes by plasmochin
- 4 R S Teague and Mervin Perdue (*by invitation*), *Medical College of Alabama*
The effect of anesthetics and cerebral vasodilating procedures on the penetration of sulfathiazole into the cerebro-spinal fluid
- 5 Charles W Mushett and Harrison S Martland (*introduced by* Hans Molitor), *Merck Institute for Therapeutic Research and City Hospital of Newark*
Anatomic changes produced by streptothricin

- 6 J T Litchfield, Jr, L Alonso, and L Goddard, *Chemotherapy Division, Stamford Research Laboratories, American Cyanamid Company*

Determination of minute quantities of sulfanilamide derivatives in biological samples

- 7 Gladys A Emerson and D G Smith (*introduced by Hans Mohr*), *Merck Institute for Therapeutic Research*

A comparison of the effects of streptomycin in the nutrition of the rat and the mouse

PHARMACOLOGY B

Thursday, 9 00 a m

COMMITTEE ROOM 1

Antispasmodics

- 1 Bradford N Craver (*by invitation*), Patricia Seip (*by invitation*), Anne Cameron (*by invitation*), (*introduced by Frederick F Yonkman*), *Ciba Pharmaceutical Products, Inc*
A simple method of recording uterine motility in vivo

- 2 R A Woodbury, George P Child (*by invitation*), Richard Torpin (*by invitation*), Walter Watson (*by invitation*), and Louise Jarboe (*by invitation*), *University of Georgia School of Medicine*

Electro uterography and the physiology of the human uterus as related to dysmenorrhea and metrorrhagia

- 3 George P Child (*by invitation*), R A Woodbury, Richard Torpin (*by invitation*), Walter G Watson (*by invitation*), and Louise Jarboe (*by invitation*), *University of Georgia School of Medicine*

The irritability of the human uterus as affected by various drugs

- 4 Russell A Huggins (*by invitation*) and R A Woodbury, *University of Georgia School of Medicine*

Evaluation of uterine antispasmodics

- 5 T J Becker, Estelle Ananenkov (*by invitation*), Gwendolyn Glenwood (*by invitation*), and L C Miller, *Winthrop Chemical Co, Inc*

The antispasmodic activity of substituted phenyl propyl piperidines

- 6 K G Wakim, Clarence E Powell (*by invitation*), and K K Chen, *Indiana University Medical Center and Lilly Research Laboratories*

Effects of B dimethylaminoethyl benzilate HCl on intestinal activity

- 7 G L Cantoni and G Eastman (*by invitation*), *Long Island College of Medicine and New York University College of Medicine*

On the specificity of histamine and on the rôle of potassium in a loss of contractility of the intestinal smooth muscle of the guinea pig

- 8 Clara Torda and Harold G Wolff, *New York Hospital and the Departments of Medicine (Neurology) and Psychiatry, Cornell University Medical College*

Studies on myasthenia gravis apparent "curare-like" effect of compounds that decrease acetylcholine synthesis

PHARMACOLOGY C

Thursday, 9 00 a m

COMMITTEE ROOM 2

Metabolism and Drugs

- 1 Dorothy Fulghum (*by invitation*), Dorothy Fitzwater (*by invitation*), and O S Gibbs, *Memphis*

The effect of xanthines and pituitrin on water loss

- 2 O S Gibbs and Dorothy Fulghum (*by invitation*), *Memphis*

The diuretic antidiuretic actions of posterior pituitary and sodium chloride

- 3 Frederick Bernheim (*with the technical assistance of Helen R Field*), *Duke Medical School*

The effect of methyl xanthines on urea excretion in rabbits

- 4 Herbert Tabor (*by invitation*) and Sanford M Rosenthal, *Division of Physiology, National Institute of Health*

Depression of metabolism and temperature in traumatic shock as evidence of a toxic factor

- 5 Frederick Sperling (*by invitation*), *Georgetown University School of Medicine*

Detection of oxidation-reduction by alkaline solutions of methylene blue and orcein

- 6 A J Lehman, *University of North Carolina Medical School*

The effect of insulin, insulin-dextrose, and water diuresis on the metabolism of isopropyl alcohol

- 7 Edward Larson, *Temple University School of Medicine*

The effect of pentobarbital sodium, evipal sodium and demerol on the action of insulin

- 8 R Lorimer Grant (*introduced by John H Draize*), *Food and Drug Administration, Federal Security Agency*

Loss of potency of commercial insulin stored at room temperature

- 9 William M Govier, Mary E Grellis, Naomi Lanz, and Karl H Beyer, *Medical Research Division, Sharp and Dohme, Inc*

The oxidation of tyramine in vitro

- 10 Jean K Fellows (*by invitation*) and F P Ludueña, *Stanford University School of Medicine*

Glucuronic acid excretion after various glycols

PHARMACOLOGICAL SOCIETY BUSINESS MEETING

Thursday, 11 00 a m

Room 9

JOINT SESSION OF THE PHARMACOLOGY AND BIOCHEMICAL SOCIETIES ON DIISOPROPYL FLUOROPHOSPHATE (DFP)

Thursday, 2 00 p m

BALLROOM

- 1 Oscar Bodansky and Abraham Mazur, *Biochemistry Section, Medical Division, Chemical Warfare Service, Edgewood Arsenal*
The mechanism of *in vitro* and *in vivo* inhibition of cholinesterase activity by diisopropyl fluorophosphate (DFP)
- 2 Abraham Mazur, *Biochemistry Section, Medical Division, Chemical Warfare Service, Edgewood Arsenal*
An enzyme in the animal organism capable of hydrolyzing diisopropyl fluorophosphate (DFP)
- 3 George B Koelle (by invitation) and Alfred Gilman, *Pharmacology Section, Medical Division, Chemical Warfare Service, Edgewood Arsenal*
The chronic toxicity of diisopropyl fluorophosphate (DFP) in dogs, monkeys and rats
- 4 Walter F Riker and William C Wescoe (introduced by McKeen Cattell), *Cornell University Medical College*
Comparative studies on the nicotinic action of diisopropyl fluorophosphate (DFP)
- 5 Rudolph Koster (introduced by McKeen Cattell), *Cornell University Medical College*
The synergistic and antagonistic effects of diisopropyl fluorophosphate (DFP) and physostigmine in the cat
- 6 M A Rothenberg and D Nachmansohn (introduced by H T Clarke), *Departments of Neurology and Biochemistry, College of Physicians and Surgeons, Columbia University*
On the permeability of the nerve axon to diisopropyl fluorophosphate (DFP)
- 7 Frederick Crescitelli (by invitation), George B Koelle (by invitation), and Alfred Gilman, *Pharmacology Section, Medical Division, Chemical Warfare Service, Edgewood Arsenal*
Nerve conduction in absence of cholinesterase activity induced by diisopropyl fluorophosphate (DFP)

- 8 A McGehee Harvey, Benjamin F Jones, Samuel Talbot, and David Grob (introduced by Oscar Bodansky), *The Johns Hopkins Medical School*
The effect of diisopropyl fluorophosphate (DFP) on neuromuscular transmission in normal individuals and in patients with myasthenia gravis

- 9 J H Comroe, Jr, J Todd (by invitation), George Gammon (by invitation), George Koelle (by invitation), and Alfred Gilman, *University of Pennsylvania Medical School and Pharmacology Section, Medical Division, Chemical Warfare Service, Edgewood Arsenal*
The effect of diisopropyl fluorophosphate (DFP) on normal men and patients with myasthenia gravis
- 10 I H Leopold (by invitation) and J H Comroe, Jr, *University of Pennsylvania Medical School*
The effect of diisopropyl fluorophosphate (DFP) on the normal and glaucomatous eye

PHARMACOLOGY A

Friday, 9 00 a m

Room 9

- ### Chemotherapy, Malaria and Bacterial Infections
- 1 H J White, M E Lee, E R Jackson, A T Himes, and C Alverson (introduced by J T Litchfield, Jr), *Chemotherapy Division, Stamford Research Laboratories, American Cyanamid Company*
Pantoyltauramides as antibacterial chemotherapeutic agents
 - 2 M I Smith, Wm T McClosky, and E W Emmart (by invitation), *Division of Physiology, National Institute of Health*
The influence of streptomycin and promin on the proliferation of tubercle bacilli in the tissues of the albino rat
 - 3 Gladys A Emerson and Eder Lindsay Hansen (introduced by Hamilton H Anderson), *University of California Medical School*
Growth requirements of *Endameba histolytica*
 - 4 Rachael K Reed, Josephine Mar, and Hamilton H Anderson, *University of California Medical School*
Comparative toxicity and efficacy of "urea stibamines" in experimental leishmaniasis
 - 5 Harry A Feldman, Henry Packer (by invitation), Franklin D Murphy (by invitation), and Robert Briggs Watson (by invitation), *University of Tennessee College of Medicine and Safety Department, Tennessee Valley Authority*
Pamaquine naphthoate as a prophylactic for malarial infections (*Immunol*)

- 6 F E Kelsey, Frances K Oldham, and A L Gittelson, *University of Chicago*
Studies on antimalarial drugs curative effect of plasmoquin in *Plasmodium lophurae* infections
- 7 Harry A Walker (by invitation) Leslie A Stauber (by invitation), and Arthur P Richardson, *The Squibb Institute for Medical Research*
Pamaquine naphthoate, quinacrine hydrochloride, and quinine bisulfate as curative agents in *Plasmodium cathemerrum* infections of the duck
- 8 Arthur P Richardson, R I Hewitt (by invitation), L D Seager, M M Brooke (by invitation), F Martin, and H Maddux (by invitation), *University of Tennessee and The Squibb Institute for Medical Research*
Chemotherapy of *Plasmodium knowlesi* infections in *macaca mulatta* monkeys
- 9 Alf S Alving, Lillian Eichelberger, Branch Craige, Jr (by invitation), Ralph Jones, Jr (by invitation), Theodore Pullman (by invitation), C Merrill Whorton, *The Malarial Research Unit, The University of Chicago Department of Medicine*
A comparison of the clinical antimalarial properties and toxicity of several 8 amino quinolines using plasmoquin as a standard of reference (*Physiol*)
- 10 Branch Craige, Jr (by invitation), Ralph Jones, Jr (by invitation), Theodore Pullman (by invitation), C Merrill Whorton (by invitation), Lillian Eichelberger, and Alf S Alving, *The Malarial Research Unit, University of Chicago Department of Medicine*
Clinical standardization of the antimalarial properties and the toxicity of plasmoquin administered alone and concurrently with quinine (*Physiol*)
- 11 Richard J Porter (by invitation) and John W Bean, *University of Michigan*
Adverse influence of increased oxygen pressure on malarial parasites in vitro and in vivo (*Physiol*)
- 12 Clyde Brooks, *Essex College of Medicine and Surgery*
Chemotherapy of tuberculosis I thymol in experimental tuberculosis in the guinea pig

PHARMACOLOGY B

Friday, 9:00 a m

COMMITTEE ROOM 1

Cardiac and Related Drugs

- 1 James A Richardson (by invitation) and R P Walton, *Medical College of South Carolina*

- Absence of significant changes in blood coagulability during digitalization
- 2 G Maresh and A Farah (introduced by O Krayner), *Harvard Medical School*
Toxicity ratios of some cardiac glycosides as influenced by the experimental time
- 3 A Farah (by invitation) and O Krayner, *Harvard Medical School*
The action of dimethylamino ethanol upon the heart-lung preparation of the dog
- 4 Helen J Danow (by invitation), Donald R Matheson (by invitation), Harry W Hays (by invitation) (introduced by E Oppenheimer), *Ciba Pharmaceutical Products, Inc*
Comparison of a chemical and a biological method for the assay of a purified digitalis preparation
- 5 William T Salter and Walter F White (by invitation), *Yale University School of Medicine*
The response of "fatigued" myocardium to known concentrations of a cardiac glycoside
- 6 Stephen Krop and Wallace F White (by invitation), *Yale University School of Medicine*
The effect of coumestrol on the contractile force of isolated mammalian cardiac muscle
- 7 Graham Chen, E M K Geiling, and J Reilly, *The University of Chicago*
Electrocardiographic changes of rats, dogs and monkeys receiving toxic doses of plasmoquin and the acid-labile phosphate content of the rat's myocardium
- 8 O S Orth and Roland R Liebenow (by invitation), *University of Wisconsin Medical School*
The mechanism of action of chloroform on the heart
- 9 K I Melville, *McGill University*
The protective action of atabrine against chloroform adrenaline ventricular fibrillation
- 10 Harry Gold, Walter Modell, Harold L Otto (by invitation), and Lawrence W Hanlon (by invitation) (with the technical assistance of Jenny Oppenheim, by invitation), *Cornell University Medical College and Cardiac Services of the Beth Israel Hospital and Hospital for Joint Diseases*
Comparison of cinchona alkaloids on the circus rate of the auricle in patients with auricular fibrillation
- 11 Walter Modell, Harry Gold, and Donald A Clarke (by invitation), *Cornell University Medical College and Cardiac Services of the Beth Israel Hospital and Hospital for Joint Diseases*
Dosage-response to mercurhydrin in patients with heart failure

PHARMACOLOGY C

Friday, 9 00 a m

COMMITTEE ROOM 2

Sympathetic and Related Drugs

- 1 Raymond P Ahlquist and R A Woodbury, *University of Georgia School of Medicine*
The influence of benzyl-imidazoline (prisco) on sympathomimetic vasoconstrictors and vasodilators
- 2 Amedeo S Marrazzi and Rose N Marrazzi, *Wayne University College of Medicine*
Inhibitory potency of sympathomimetic amines and their ganglionic inhibitory action
- 3 Fred W Ellis and James F Newsome (by invitation), *University of North Carolina*
The effect of certain new antihistamine drugs on bronchial spasm
- 4 T R Sherrod, H F Schloemer, and E R Loew (introduced by C C Pfeiffer), *University of Illinois College of Medicine*
Pharmacological studies on anti-histamine compounds
- 5 E R Loew, Margaret E Kaiser, and Mona Anderson (introduced by Carl C Pfeiffer), *University of Illinois College of Medicine and Parke, Davis and Company*
The anti - histamine and atropine - like properties of quaternary ammonium derivatives of benadryl
- 6 W A Selle, *University of Texas Medical School*
Beta dimethylamino-ethyl benzhydryl ether hydro-chloride as an antihistamine and anti-anaphylactic agent (*Physiol*)
- 7 Irvine H Page and Arda Alden Green (by invitation), *Research Division of the Cleveland Clinic Foundation*
The vascular action of B-dimethylaminoethyl benzhydryl ether-hydrochloride (benadryl) (*Physiol*)
- 8 Mark Nickerson (by invitation) and Louis S Goodman, *University of Utah School of Medicine*
Physiological properties of a new series of sympatholytic agents
- 9 Frederick F Yonkman, Dorothy Chess (by invitation), Harry W Hays (by invitation), Barbara Rennick (by invitation), and Rudolf Mayer (by invitation), *Ciba Pharmaceutical Products, Inc*
Adrenergic potentiation by pyribenzamine HCl (N'-pyridyl-N'-benzyl-N-dimethylethylenediamine HCl)
- 10 George F Koepf, Carl E Arbesman (by invitation), and Alfred Lenzner (by invitation),

University of Buffalo and the Buffalo General Hospital

Evidence of a synergism between pyribenzamine HCl and sympathetic mimetic drugs in humans (*Physiol*)

- 11 S A Pereira (by invitation) and G H Acheson, *Harvard Medical School*
Action of tetraethyl ammonium bromide on the superior cervical ganglion
- 12 G H Acheson and S A Pereira (by invitation), *Harvard Medical School*
Action of tetraethyl ammonium bromide on the mammalian neuromuscular system

PAPERS READ BY TITLE

PHARMACOLOGY

- 1 Robert C Anderson (by invitation) and K K Chen, *Lilly Research Laboratories*
The action of fumariaceous alkaloids
- 2 T C Barnes and R Beutner, *Hahnemann Medical College and Hospital of Philadelphia*
Mechanism of action of calcium on the nervous system
- 3 Robert W Berliner (introduced by James A Shannon), *Third Medical Division, Goldwater Memorial Hospital, and New York University College of Medicine*
In vitro development of *P falciparum* gametocytes
- 4 Robert W Berliner (introduced by James A Shannon), *Third Medical Division, Goldwater Memorial Hospital, and New York University College of Medicine*
The in vitro assay of suppressive antimalarial activity *P falciparum*
- 5 Robert W Berliner (introduced by James A Shannon), Frederick S Bigelow (by invitation), Thomas J Kennedy, Jr, *Third Medical Division, Goldwater Memorial Hospital, and New York University College of Medicine*
Concentration technique for detection of trophozoites of human malaria
- 6 Robert W Berliner (by invitation), John V Taggart (by invitation), Charles G Zubrod (by invitation), William J Welch (by invitation), David P Earle, Jr (by invitation), and James A Shannon, *Third Medical Division, Goldwater Memorial Hospital, and New York University College of Medicine*
Pamaquin 1 Curative antimalarial activity in vivax malaria
- 7 R Beutner, *Hahnemann Medical College*
The cardiac toxicity of injectable local anesthetics
- 8 R Beutner and W C Dietrich (by invitation), *Hahnemann Medical College*
The blood pressure lowering effect of local anesthetics used for injection

- 9 R Beutner and W C Dietrich (*by invitation*),
Hahnemann Medical College and Hospital of Philadelphia
The least irritant of the commonly used topical anesthetics
- 10 Graham Chen and E M K Geiling, *The University of Chicago*
The effect of thiamine-deficiency, quinidine, hyperthyroidism and hypothyroidism on the adenosine-triphosphate content and the adenosine-triphosphatase activity of the heart muscle of rats
- 11 Graham Chen and E M K Geiling, *The University of Chicago*
The joint toxicity of atabrine and quinine, atabrine and plasmochin, quinine and plasmochin
- 12 Graham Chen, F Schueler and E M K Geiling, *The University of Chicago*
The effect of adenosine triphosphate on the isolated heart
- 13 K K Chen, Paul N Harris and Robert C Anderson (*by invitation*), *Lilly Research Laboratories*
Antithyroid activity of 24 compounds
- 14 John Emerson Davis, *University of Arkansas*
The anemia produced by paraphenylenediamine in dogs
- 15 W C Dietrich (*by invitation*) and R Beutner, *The Hahnemann Medical College and Hospital of Philadelphia*
Failure of o- or p-mononitrophenol to produce cataract
- 16 David P Earle, Jr (*by invitation*), Peter Knowlton (*by invitation*), Robert W Berliner (*by invitation*), John V Taggart (*by invitation*), Charles G Zubrod (*by invitation*), William J Welch (*by invitation*), and James A Shannon, *Third Medical Division, Goldwater Memorial Hospital, and New York University College of Medicine*
Pamaquin 3 Occurrence of hemolytic anemias
- 17 Louis S Goodman, Ewart A Swinyard (*by invitation*), and James E P Toman, *University of Utah School of Medicine*
Studies on the anticonvulsant properties of diphenylhydantoin
- 18 Stephen Krop, *Yale University School of Medicine*
The effect of nephrectomy on the "elimination" of ouabain by the cat
- 19 Stephen Krop, *Yale University School of Medicine*
The effect of succinate on pentobarbital toxicity and narcosis in the cat
- 20 Mark Nickerson (*by invitation*), George Nomaguchi (*by invitation*), and Louis S Goodman, *University of Utah School of Medicine*
Relation of structure to activity in a new series of sympatholytic agents
- 21 Mark Nickerson and Scott M Smith (*by invitation*) and Louis S Goodman, *University of Utah School of Medicine*
The prevention of epinephrine cyclopropane cardiac irregularities in dogs with dibenzyl-B chloroethyl amine
- 22 Mark Nickerson, Thomas Burns, and Arnold M Cooper (*introduced by Louis S Goodman*), *University of Utah School of Medicine*
Effect of anti reticular cytotoxic serum (ACS) on the healing of experimental wounds in rats
- 23 O S Orth, *University of Wisconsin Medical School*
Studies of the sympatholytic drug dihydroxyergotamine (D H E 45)
- 24 Charles C Scott and K K Chen, *Lilly Research Laboratories*
Insulin resistance in owls
- 25 Donald Slaughter, Jabez Galt and Jane C Neff, *Southwestern Medical College*
Studies on bromaspirin
- 26 M I Smith, E L Jackson (*by invitation*) and Wm T McClosky, *Division of Physiology, National Institute of Health*
Further observations on the action of sulfones in experimental tuberculosis, chemical constitution and chemotherapeutic action
- 27 Paul K Smith and Helen L Gleason, *Department of Pharmacology and Biochemistry, Randolph Field AAF School of Aviation Medicine*
Determination of salicylate fractions in urine following the administration of salicylates
- 28 Ewart A Swinyard (*by invitation*) and Louis S Goodman, *University of Utah School of Medicine*
Laboratory assay of anticonvulsant potency of some hydantoins
- 29 John V Taggart (*introduced by James A Shannon*), *Third Medical Division, Goldwater Memorial Hospital, and New York University College of Medicine*
The physiological disposition of a series of 9 amino acridines
- 30 John V Taggart (*by invitation*), Robert W Berliner (*by invitation*), Charles G Zubrod (*by invitation*), William J Welch (*by invitation*), David P Earle, Jr (*by invitation*), and James A Shannon, *Third Medical Division, Goldwater Memorial Hospital, and New York University College of Medicine*
Pamaquin 2 Suppressive antimalarial activity in *vivax* and *falciparum* malaria
- 31 James E P Toman, Louis S Goodman and Ewart A Swinyard (*by invitation*), *University of Utah School of Medicine*

- Observations on the central excitatory effects of metrazol
- 32 H B van Dyke and Alfred Gellhorn (*by invitation*), *College of Physicians and Surgeons, Columbia University*
Chemotherapeutic studies in experimental leishmaniasis
- 33 William J Welch, Peter Knowlton, Frederick S Bigelow, Eli Bauman, and Robert W Berliner (*introduced by James A Shannon*), *Third Medical Division, Goldwater Memorial Hospital, and New York University College of Medicine*
The incidence of convulsions in general paresis receiving quinacrine
- 34 Abraham Wikler, *Research Department, U S Public Health Service Hospital*
Effects of a cycle of morphine addiction on conditioned responses and experimental neuroses in dogs
- 35 Frederick F Yonkman, Harry W Hays (*by invitation*), Anne Cameron (*by invitation*), Elizabeth Pellett (*by invitation*), and Nicoline Hansen (*by invitation*), *Ciba Pharmaceutical Products, Inc*
Cholinergic action of the anti-sympathetic agent priscol (benzylimidazoline HCl)
- 36 Charles G Zubrod (*by invitation*), Peter Knowlton (*by invitation*), William J Welch (*by invitation*), Robert W Berliner (*by invitation*), John V Taggart (*by invitation*), David P Earle, Jr (*by invitation*), and James A Shannon, *Third Medical Division, Goldwater Memorial Hospital, and New York University College of Medicine*
Pamaquin 4 Occurrence of leucopenia

PATHOLOGY

Tuesday, 9 00 a m

Room 17

Neoplasms

- 1 Leroy U Gardner and H F Heslington (*by invitation*), *The Saranac Laboratory for the Study of Tuberculosis*
Osteo-sarcoma from intravenous beryllium compounds in rabbits
- 2 Floyd DeEds and Robert H Wilson, *Pharmacology Division, Bureau of Agricultural and Industrial Chemistry, U S Department of Agriculture*
The carcinogenic activity of 2-acetamino-fluorene effects of concentration and duration of exposure (*Pharm*)
- 3 Robert H Wilson and Floyd DeEds, *Pharmacology Division, Bureau of Agricultural*

and Industrial Chemistry, U S Department of Agriculture

- The carcinogenic activity of various fluorene derivatives (*Pharm*)
- 4 George R Sharpless, *Department of Laboratories, Henry Ford Hospital, Detroit*
The effects of copper on liver tumor induction by p dimethylaminoazobenzene (*Nutr*)
- 5 C W Sheppard (*by invitation*) and P F Hahn, *Vanderbilt University, Nashville*
Studies of radioactive methods of the distribution, retention and excretion of colloidal particles administered intravenously in humans
- 6 Paul F Hahn and C W Sheppard (*by invitation*), *Vanderbilt University, Nashville*
The selective radiation of specific tissues and viscera by means of radioactive isotopes
- 7 Warner F Sheldon (*by invitation*) and Dale R Coman, *University of Pennsylvania*
The significance of hyperemia around tumor implants
- 8 Lyle V Beck, *Hahnemann Medical College, Philadelphia*
The Shear tumor necrotizing bacterial polysaccharide as a pyrogen (*Physiol*)

PATHOLOGY

Tuesday, 2 00 p m

Room 17

Injury and Repair, Viruses

- 1 H F Blum and W S Terus (*by invitation*), *Naval Medical Research Institute, Bethesda*
Inhibition of erythema of sunburn by large doses of ultraviolet radiation (*Physiol*)
- 2 Hiram E Essex and Alfonso Graña (*by invitation*), *Mayo Foundation, Rochester, Minn*
A method of observing transient leucopenia (*Physiol*)
- 3 Valy Menkin, E Ulled (*by invitation*) and E G Goodman (*by invitation*), *Duke University School of Medicine*
Effects of the leukocytosis-promoting factor of exudates on human beings
- 4 Jacob Chandy and Jonathan E Rhoads (*introduced by I S Ravdin*), *University of Pennsylvania*
Experimental studies on the mechanism of the formation of intraperitoneal adhesions
- 5 O M Gruhzit, *Research Laboratories, Parke, Davis & Company*
Oxidized cellulose absorption and histopathology
- 6 Glenn H Algire, *National Cancer Institute, U S Public Health Service*

Effect of a bacterial polysaccharide and of
tourniquet shock on peripheral capillary
circulation in unanesthetized mice

- 7 M B Andelman (*by invitation*), William I
Fishbein (*by invitation*) and Albert E Casey,
*Laboratories of Chicago Health Department
and the Birmingham Baptist Hospitals*

Spinal fluid protein in the retrospective
diagnosis of sub-clinical poliomyelitis

- 8 Clayton G Loosli, *University of Chicago and
Commissions on Influenza and Air-borne
Infections, Army Epidemiological Board,
Office of Surgeon General, A U S*

The pathogenesis and pathology of experi-
mental air-borne influenza A virus infection
in mice

- 9 T L Rights (*by invitation*), E B Jackson (*by
invitation*) and J E Smadel, *Division of
Virus and Rickettsial Diseases, Army
Medical School, Washington*

Observations on Tyzzer's disease of mice

BUSINESS MEETING TO FOLLOW PAPER NO 9

PATHOLOGY

Wednesday, 9 00 a m

Room 17

Hematology, Nutrition

- 1 Reubenia Dubach (*by invitation*), Carl V
Moore and Virginia Minnich (*by invitation*),
Washington University, St Louis, Mo

Studies on the rate and completeness with
which intravenously injected radioactive
iron is utilized

- 2 L B Jaques, E Fidler (*by invitation*), E T
Feldsted (*by invitation*) and A G Mac-
Donald (*by invitation*), *University of Toronto
and University of Manitoba*

Silicones and blood coagulation (*Physiol*)

- 3 J R Carter (*by invitation*) and H P Smith,
*Slate University of Iowa and Columbia
University*

The existence of variations in the ease with
which thrombin preparations may be inacti-
vated by antithrombin

- 4 Nathan B Friedman and Kurt Lange (*by
invitation*), *Army Institute of Pathology,
Washington, D C, N Y Medical College,
Flower and Fifth Avenue Hospitals, and the
Metropolitan Hospital Research Unit*

The pathology of experimental frostbite

- 5 Hans Kaunitz (*introduced by H P Smith*),
Columbia University

Influence of single doses of alpha tocopherol
on growth and testicular atrophy of rats

- 6 Paul R Cannon, Robert W Wissler (*by invita-
tion*), C Harold Steffee, Jr (*by invitation*),
Robert L Straube (*by invitation*) and Lau-
rence E Frazier (*by invitation*), *University
of Chicago*

The influence of the essential amino acids
upon appetite in protein-depleted adult
white rats

- 7 F S Robschert-Robbins and L L Miller
(*by invitation*), *School of Medicine and
Dentistry, University of Rochester*

Amino acid utilization in simultaneous hypo-
proteinemia and anemia Elimination of one
essential from growth mixture (*Rose*)

- 8 Jesse L Bollman and Eunice V Flock (*by
invitation*), *Mayo Foundation, Rochester,
Minn*

Dietary influence on phospholipid turnover
in liver and plasma

- 9 Louis D Greenberg (*by invitation*) and James
F Rinehart, *University of California Medical
School*

Studies on pyridoxine deficiency in rhesus
monkeys

PATHOLOGY

Wednesday, 2 00 p m

Room 17

- 1 Thelma B Dunn and C Donald Larsen (*by
invitation*), *National Cancer Institute, Beth-
esda, Md*

Hyalinization of glomeruli produced in strain
A mice by the administration of urethane
(ethyl carbamate)

- 2 Hans F Smetana, *Columbia University*
The permeability of renal glomeruli for pro-
teins in lower animals

- 3 Arthur M Ginzler (*introduced by Arnold R
Rich*), *Chemical Warfare Service, Edgewood
Arsenal, Maryland*

The effect of BAL therapy on the renal lesion
in mercury poisoning

- 4 Russell L Holman, *University of North
Carolina*

Prevention of experimental arterial lesions
by cholesterol

- 5 W C Hueper, *Warner Institute for Thera-
peutic Research, New York*

Experimental jugular phlebitis

- 6 Ward J MacNeal, Anne Blevins (*by invitation*),
Alice C Slavkin (*by invitation*) and Helen
Scanlon (*by invitation*), *N Y Post Graduate
Medical School and Hospital, Columbia
University*

Experimental non bacterial cardiovascular
inflammation

- 7 G R Meneely, Mildred Stahlman, F R
McCrea L E Smith and H J Smith (*intro-*

duced by E W Goodpasture), *Vanderbilt University, Nashville*

Ischemic and anoxic damage to myocardial capillaries and its relation to shock, angina pectoris and myocardial infarction

- 8 David A Karnofsky (*by invitation*), Irving Graef and Homer W Smith (*by invitation*), *New York University College of Medicine*
Studies on the mechanism of production of systemic injury by di-b-chloroethylmethylamine hydrochloride

- 9 Irving Graef, David A Karnofsky (*by invitation*), Val B Jager (*by invitation*) and Homer W Smith (*by invitation*), *New York University College of Medicine*

The clinical and pathologic effects of the vesicant nitrogen and sulfur mustards

- 10 Arild E Hansen and Hilda F Wiese (*by invitation*), *University of Texas School of Medicine*

Tissue lipids in essential xanthomatosis

- 11 Stephen Maddock and Dorothy Jensen (*by invitation*), *Surgical Research Laboratory, Boston City Hospital, Boston*

Liver function tests from a surgical point of view

PATHOLOGY

Wednesday, 9 00-12 00 a m —2 00-5 00 p m

JOINT MEETING WITH THE AMERICAN ASSOCIATION OF IMMUNOLOGISTS

(See program of Immunology for details)

PAPER READ BY TITLE

PATHOLOGY

Nellie Halliday (*by invitation*) and Charles Weiss, *University of California, Mt Zion Hospital, San Francisco, Jewish Hospital, Philadelphia, Pa*

Effect of biotin and other B vitamins on proteinases

NUTRITION

Tuesday, 9 00 a m

BALLROOM

SYMPOSIUM ON APPLICATIONS OF THE NEWER KNOWLEDGE OF NUTRITION TO PRESENT-DAY PROBLEMS

W C Rose, *Chairman*

- 1 Frank G Boudreau, *Chairman, Food and Nutrition Board*

The Food and Nutrition Board of the National Research Council A review of some of its

accomplishments and a forecast of its future

- 2 L A Maynard, *Cornell University*
International food evaluation activities and problems
- 3 W E Krauss, *Ohio Agricultural Experiment Station*
Nutritional aspects of the milk supply
- 4 P C Jeans, *University of Iowa*
Human dietary allowances
- 5 C A Elvehjem, *University of Wisconsin*
The significance and limitation of food composition tables

NUTRITION

Tuesday, 2 00 p m

Room 10

General

- 1 David B Dill, *Fatigue Laboratory, Harvard University, Boston, Mass*
Problems of world nutrition
- 2 Ernest E Lockhart (*by invitation*), Francisco de P Miranda (*by invitation*), and Robert S Harris, *Nutritional Biochemistry Laboratories, Massachusetts Institute of Technology, Cambridge, and National Institute of Nutrition, Mexico*
The nutritional status of school children in Mexico City
- 3 Una L Robinson (*introduced by Marianne Goettsch*) and Ramón Suárez (*introduced by Marianne Goettsch*), *Nutrition Research Laboratory, Department of Medicine, School of Tropical Medicine, San Juan, Puerto Rico*
Nutrition survey in Puerto Rico
- 4 Barnett Sure, *Department of Agricultural Chemistry, University of Arkansas, Fayetteville*
Nutritional improvement of cereal flours and cereal grains I
- 5 David K Bosshardt (*by invitation*) and Richard H Barnes, *Department of Biochemical Research, Sharp and Dohme, Inc, Glenolden, Pa*
Caloric intake and the utilization of dietary protein for growth
- 6 Gladys Stevenson (*by invitation*), Pearl P Swanson, Wanda Willman (*by invitation*) and Miriam Brush (*by invitation*), *The Nutrition Laboratory, The Foods and Nutrition Section, Iowa Agricultural Experiment Station, Ames*
Nitrogen metabolism as influenced by level of caloric intake, character of diet, and nutritional state of animal

- 7 Philip Handler (introduced by W J Dann),
*Department of Biochemistry, Duke University
School of Medicine, Durham, North Carolina*
The failure of skeletal calcification produced
by high lactose diets and by simple caloric
restriction

- 8 James M Orten and Judith Mackey Keller
(by invitation), *Department of Physiological
Chemistry, Wayne University College of
Medicine, Detroit*

Dietary protein and porphyrin metabolism in
the rat

- 9 William J Darby, Paul F Hahn (by invitation),
Ruth C Steinkamp (by invitation), and
Margaret M Kaser (by invitation), *Depart-
ments of Biochemistry and Medicine, School
of Medicine, Vanderbilt University, Nash-
ville, Tennessee*

Absorption of radioactive iron by school
children

- 10 T H Jukes, A C Dornbush (by invitation),
and J J Oleson (by invitation), *Lederle
Laboratories, Pearl River, New York*

Further observations on choline and related
compounds in nutrition

- 11 7 30 p m —Business meeting

NUTRITION

Wednesday, 9 00 a m

Room 10

Vitamins

- 1 Carl V Moore, Olga S Bierbaum (by invita-
tion), Robert W Heinle (by invitation),
and Arnold D Welch, *Schools of Medicine
of Washington University, St Louis, and
Western Reserve University, Cleveland, and
their Associated Hospitals*

Studies of L casei factor ("folic acid") in
macrocytic anemias

- 2 Floyd S Daft and W H Sebrell, *Division of
Physiology, National Institute of Health,
Bethesda, Maryland*

An unidentified factor or factors effective in
the treatment of experimental blood dys-
crasias in rats

- 3 Grace A Goldsmith, *Department of Medicine,
Tulane University School of Medicine, New
Orleans, Louisiana*

The effect of folic acid on the blood picture in
human macrocytic anemia

- 4 Susan Gower Smith, *Department of Medicine,
Duke University School of Medicine, Dur-
ham, North Carolina*

Further studies on dogs with the progressive
paralysis which responds to biotin

- 5 Gladys A Emerson and J C Keresztesy,
*Merck Institute for Therapeutic Research
and the Research Laboratories of Merck
and Co, Inc, Rahway, N J*

Biotin deficiency produced by the feeding of
Marfanil to rats

- 6 D W Woolley, *The Rockefeller Institute for
Medical Research, New York*

Some relationships between the nutritive
properties and the streptogenin contents of
proteins

- 7 Jack M Cooperman (by invitation), Keith
B McCall (by invitation), W R Ruegamer
(by invitation) and C A Elvehjem, *Depart-
ment of Biochemistry, University of Wis-
consin, Madison*

Attempts to produce a niacin deficiency in
the monkey

- 8 L R Richardson and A G Hogan, *Department
of Agricultural Chemistry, University of
Missouri, Columbia*

Diet of mother and hydrocephalus in infant
rats

- 9 Helen R Skeggs and Lemuel D Wright (intro-
duced by Richard H Barnes), *Nutritional
Laboratories, Department of Pharmacology,
Medical Research Division, Sharp and
Dohme, Inc, Glenolden, Pa*

Vitamin B complex studies with diets differing
in the carbohydrate component

- 10 James H Jones, Claire Foster (by invitation)
and Werner Henle (by invitation), *Depart-
ments of Physiological Chemistry and Pedi-
atrics, University of Pennsylvania, and
Children's Hospital of Philadelphia, Phila-
delphia*

A study of the influence of various dietary
deficiencies on the response of mice to the
virus of poliomyelitis

- 11 Harry M Vars and Julius Schultz (by invita-
tion), *Harrison Department of Surgical
Research, University of Pennsylvania, School
of Medicine, Philadelphia*

Realimentation gain of rats on protein fat
diets as affected by various liver supple-
ments

NUTRITION

Wednesday, 2 00 p m

Room 10

Vitamins

- 1 Helen Oldham (by invitation), Elizabeth
Lounds (by invitation) and Thelma Porter,
*Department of Home Economics, University
of Chicago, Chicago, Ill*

Riboflavin excretions and test dose returns of
young women during periods of positive and
negative nitrogen balances

- 2 Wilma Brewer (*by invitation*), Thelma Porter, Ruth Ingalls (*by invitation*), Marie Dye and Margaret Ohlson, *Department of Foods and Nutrition, School of Home Economics, Michigan State College, East Lansing*
Urinary excretion of riboflavin by college women

- 3 Charlotte Roderuck (*by invitation*), Harold H Williams and Icie G Macie, *Research Laboratory, Children's Fund of Michigan*
Utilization of thiamine and riboflavin by lactating women

- 4 Helen T Ness (*by invitation*), Fung H Fung (*by invitation*) and Helen T Parsons, *Department of Home Economics, University of Wisconsin, Madison*

Further studies on the availability to human subjects of thiamin from yeasts

- 5 M C Kik, *University of Arkansas, College of Agriculture, Fayetteville*

Thiamine in parboiled rice ✓

- 6 V P Sydenstricker, W K Hall (*by invitation*), C W Hock (*by invitation*) and A P Briggs (*by invitation*), *Departments of Medicine and Biochemistry, University of Georgia School of Medicine, Augusta*

Corneal vascularization as a sign of dietary deficiency in the rat

- 7 P B Pearson and V H Melass (*by invitation*), *Texas Agricultural Experiment Station, College Station*

The pantothenic acid content of tissues of the hen as influenced by diet

- 8 P S Sarma (*introduced by* C A Elvehjem), *Department of Biochemistry, University of Wisconsin, Madison*

Vitamin B₆ bioassay

- 9 Elizabeth C Callison (*by invitation*) and Elsa Orent Keiles, *Bureau of Human Nutrition and Home Economics, U S D A, Beltsville, Md*

The utilization of carotene from carrots by humans

- 10 M Wight Taylor and Walter C Russell, *Department of Agricultural Biochemistry, New Jersey Agricultural Experiment Station, Rutgers University, New Brunswick*

The provitamin A requirement of laying hens

NUTRITION

Thursday, 9 00 a m

Room 10

Miscellaneous

- 1 Elizabeth M Hewston (*by invitation*) and Elsa Orent Keiles, *Bureau of Human Nutrition and Home Economics, U S D A, Beltsville, Md*

Ascorbic acid and dehydroascorbic acid in raw carrots as prepared for table use

- 2 Mary E Reid (*introduced by* Helen T Parsons), *Division of Physiology, National Institute of Health, Bethesda, Md*

Metabolism of ascorbic acid by guinea pigs

- 3 E W Crampton and Barbara W Burton (*by invitation*), *Department of Nutrition, Macdonald College, McGill University, P Quebec, Canada*

The biologically determined vitamin C potency of orange juice

- 4 Ross A Gortner, Jr (*by invitation*), J S Restarski (*by invitation*) and C. M McCay, *Naval Medical Research Institute, Bethesda, Md*

Some effects of dietary oxalate on the teeth of white rats

- 5 Arild E Hansen and Hilda F Wiese (*by invitation*), *Department of Pediatrics, University of Texas School of Medicine, Galveston*

Tissue lipids in child with chylous ascites maintained on low fat diet

- 6 10 00 a m—Business meeting, Presentation of Awards

PAPERS READ BY TITLE

NUTRITION

- 1 Leopold R Cerecedo, *Department of Biochemistry, Fordham University, New York, N Y*

Relationship between protein intake and pyridoxine deficiency in the rat Effect of supplementing a low-protein diet with methionine

- 2 Leopold R Cerecedo, *Department of Biochemistry, Fordham University, New York, N Y*

Strain differences in the resistance of rats to pyridoxine deficiency

- 3 Leopold R Cerecedo, Joseph G. Sandza (*by invitation*) and Edward A White (*by invitation*), *Department of Biochemistry, Fordham University, New York, N Y*

Storage of pantothenic acid in the mouse

- 4 Jerome W Conn, Margaret W Johnston and Laurence H Louis (*by invitation*), *Nutrition Laboratory, University of Michigan Medical School, Ann Arbor*

Relationship between salt intake and sweat salt concentration under conditions of hard work in humid heat

- 5 W J Dann, *Department of Physiology, Duke University School of Medicine, Durham, N C*

Effect of excess nicotinamide on growth of the chicken

- 6 W J Dann, *Department of Physiology, Duke University School of Medicine, Durham, N C*

The effect of corn grits on the nicotinic acid excretion of the rat

- 7 M C Kik, *University of Arkansas, College of Agriculture, Fayetteville*

Thiamine in soaked rice

- 8 Margaret W Johnston, Jerome W Conn, Laurence H Louis (by invitation) and Betty F Steele (by invitation), *Nutrition Laboratory, University of Michigan Medical School, Ann Arbor*

Hand sweat values in the calculation of chloride and nitrogen balance under conditions of hard work in humid heat

- 9 J F McClendon and Wm C Foster (by invitation), *Hahnemann Medical College, Philadelphia*

Growing a diet deficient in certain elements by hydroponics

- 10 Barnett Sure, *Department of Agricultural Chemistry, University of Arkansas, Fayetteville*

Nutritional improvement of cereal flours and cereal grains II

- 11 Barnett Sure, *Department of Agricultural Chemistry, University of Arkansas, Fayetteville*

Nutritional improvement of cereal flours and cereal grains III

- 12 Barnett Sure, *Department of Agricultural Chemistry, University of Arkansas, Fayetteville*

Nutritional improvement of cereal flours and cereal grains IV

- 13 Barnett Sure, *Department of Agricultural Chemistry, University of Arkansas, Fayetteville*

Nutritional improvement of cereal flours and cereal grains V

- 14 Barnett Sure, *Department of Agricultural Chemistry, University of Arkansas, Fayetteville*

Nutritional improvement of cereal flours and cereal grains VI

- 15 Barnett Sure, *Department of Agricultural Chemistry, University of Arkansas, Fayetteville*

Nutritional improvement of cereal flours and cereal grains VII

- 16 Edward A White (by invitation) and Leopold R Cerecedo, *Department of Biochemistry, Fordham University, New York, N Y*

Reproduction and lactation in mice on synthetic diets Nutritional effects of choline

- 17 Agnes Fay Morgan, Mary Groody (by invitation) and Helen E Axelrod (by invitation),

Laboratory of Home Economics, University of California, Berkeley

Carbohydrate metabolism of riboflavin-deficient dogs

- 18 Echo L Price (by invitation), Mona M Marquette (by invitation) and Helen T Parsons, *Department of Home Economics, University of Wisconsin, Madison*

Availability to human subjects of riboflavin from yeasts

IMMUNOLOGY

Tuesday, March 12, 1946

First Session, 9 15 a m (promptly)

(See Bulletin Board for location)

- 1 Jacques J Bronfenbrenner
Presidential address The nature and mode of action of bacteriophage
- 2 James A Harrison
The rôle of selection in antigenic variation of blood parasites
- 3 Gregory Schwartzman
Metabolic requirements of gram negative bacilli determining resistance to penicillin
- 4 R F Parker
Penicillin sensitivity of staphylococcus in vitro tests
- 5 Catherine E Wilson, Anne F Byrne and Carolyn W Hammond (by invitation) and Eleanor A Bliss
Effect of various routes of administration of penicillin upon experimental lobar pneumonia in rats
- 6 Geoffrey Rake and (by invitation) Dorothy Hamre
The activity of some antibiotics and sulfonamides in vitro and in vivo upon the agents of lymphogranuloma venereum and feline pneumonitis
- 7 Jules Freund and (by invitation), K J Thomson and H F Sommer
Immunization against malaria in experimental animals
- 8 Ulrich Friedemann (by invitation), A Hollander and F B Traub
Differences in the avidities of tetanal toxins for nerve tissue
- 9 Mary Hewitt Loveless
Coexistence of two antibodies for crystalline insulin in human serum
- 10 Charles Weiss (by invitation) and Nellie Halliday
The behavior of endocellular proteolytic enzymes (cathepsins) in experimental tuberculosis
- 11 T B Thomas, P L Ewing and G A Emerson (by invitation)

Effects of a bone-marrow-spleen immune serum on cytology of the spleen potentialities of a bioassay method

- 12 G A Emerson, P L Ewing and T B Thomas (by invitation)

Effects of a bone-marrow-spleen immune serum on the blood pictures in mice

Tuesday, March 12, 1946

Second Session, 2 00 p m (promptly)

(See Bulletin Board for location)

- 1 Michael Heidelberger
Antibody formation in the immunization of human beings
- 2 W E Elrich, T N Harris and E Mertens (by invitation)
The cellular sources of antibodies and other globulins
- 3 S L D'Albergo and W A Selle (by invitation)
On the membrane hypothesis of the antigen-antibody reaction
- 4 Elvin A Kabat and (by invitation) Aaron Bendich and Ada E Bezer
Immunochemical studies on blood group A substance from hog stomach
- 5 Clara Nigg (by invitation), Maurice R Hilleman and Betty M Bowser
The enhancement and properties of the complement-fixing antigens of lymphogranuloma venereum
- 6 G S Kirk, O O Stoland, C Doughty and G Boone (by invitation)
Blood studies in anaphylactic shock in dogs
- 7 Noble P Sherwood (by invitation), O O Stoland, J S Kirk and D J Temenberg
Anaphylaxis XVI Studies on passive sensitization of the dog
- 8 Kenneth L Burdon
Effect of antigen-antibody union in the circulating blood in production of anaphylactic reactions in passively sensitized mice
- 9 A W Bernheimer and G L Cantoni (by invitation)
Induction in mice of increased resistance to a lethal toxin of hemolytic streptococcus
- 10 Harry Plotz
Allergenic and anaphylactogenic properties of vaccines prepared from embryonic tissues of developing chicks I Skin sensitivity following the subcutaneous inoculation of typhus vaccines in humans
- 11 E J Coulson and Henry Stevens (by invitation)
Allergenic and anaphylactogenic properties of vaccines prepared from embryonic tissues of developing chicks II Anaphylactogenic properties of typhus fever vaccines and equine encephalomyelitis vaccine

- 12 Arthur Stull (by invitation)

Allergenic and anaphylactogenic properties of vaccines prepared from embryonic tissues of developing chicks III A study to determine whether chick yolk sac vaccines contained sufficient egg proteins to cause severe systemic reactions if given to egg-sensitive individuals

JOINT SESSION WITH THE AMERICAN SOCIETY FOR EXPERIMENTAL PATHOLOGY

Wednesday, March 13, 1946

9 15 a m (promptly)

Chairman, Wendell M Stanley

- 1 Wendell M Stanley (by invitation)
Studies on influenza virus and vaccines
- 2 Thomas Francis, Jr
Observations on influenza B in 1945
- 3 Frank L Horsfall, Jr
Viral pneumonia
- 4 Saul Makiel (introduced by Wendell M Stanley)
The composition of specific precipitates from anti-tobacco mosaic sera
- 5 Seymour S Cohen (introduced by Wendell M Stanley)
Constitution of the rickettsiae and soluble rickettsial antigen derived from the epidemic typhus vaccine
- 6 Joseph E Smadel (by invitation), J C Snyder, H L Hamilton, J P Fox and E B Jackson
Chemotherapeutic effects of nitroakridin and rutelon on rickettsial infections in eggs and mice
- 7 Herald R Cox (by invitation)
Discussion

JOINT SESSION WITH THE AMERICAN SOCIETY FOR EXPERIMENTAL PATHOLOGY

Wednesday, March 13, 1946

2 00 p m (promptly)

- 8 Peyton Rous
Biological scope of a neoplastic virus (the Shope papilloma virus)
- 9 Joseph W Beard
Characters of the rabbit papilloma virus
- 10 Howard A Howe (by invitation)
Chemical studies of cells made temporarily refractory to poliomyelitis virus
- 11 Joseph L Melnick (introduced by John R Paul)
The recovery of poliomyelitis virus from the stools of monkeys and chimpanzees experimentally infected by various routes

- 12 Albert B Sabin and R Walter Schlesinger
Experimental studies on human and mouse
adapted dengue virus
- 13 W P Havens, Jr (*introduced by John R Paul*)
Viruses of infectious hepatitis and serum
jaundice
- 14 Robert G Green
Cytotoxic properties of mouse-breast cancer
antisera

PAPERS READ BY TITLE

 IMMUNOLOGY

- Reuben L Kahn (*by invitation*), Albert H Wheeler
and Elizabeth B McDermott
Hemoglobin precipitation with tissue extract
antigen
- J Schiller, Sally Cohn (*by invitation*) and Winifred
Ashby

- Carbonic anhydrase content in the brain of rats
with thiouracil-induced cretinism
- Winifred Ashby (*by invitation*) and J Schiller
Distribution of carbonic anhydrase in the pallum
of rhesus monkey and man as compared with
that of lower mammals
- Cora M Downs (*by invitation*), Lewis L Coriell,
Gifford B Pinchot, Edward Maumenee, Alice
Klauber, L L Chapman and Barbara Owen
The comparative susceptibility of various labora-
tory animals to *B tularensis*
- P L Ewing and G A Emerson (*by invitation*)
Effects of a bone-marrow-spleen immune serum
on trypanosoma equiperdum infection in mice
- Dorothy Hamre (*by invitation*), Geoffrey Rake and
(*by invitation*) Richard Donovan
The bactericidal action of streptomycin
- Wolcott B Dunham (*by invitation*) and Geoffrey
Rake
Action of chemotherapeutic agents on the or-
ganism of granuloma inguinale

THE AMERICAN PHYSIOLOGICAL SOCIETY

FIFTY-FIFTH ANNUAL MEETING

Atlantic City, N J, March 11, 12, 13, 14, 15, 1946

For possible corrections in any of the following abstracts see the next issue

Studies on the corpus callosum and anterior commissure of monkeys HARLOW W ADES and DAVID L RAAB (by invitation) *Emory Univ* Section of the corpus callosum of monkeys has previously been reported to result in a failure of coordination of the two sides in motor activity. This is manifest in postural rigidity, extreme hesitancy of reaction and relative immobility. The defects are more profound in the absence of area 4. In either case, compensation is rapid, more so in the otherwise intact animal. The rostral half of the callosum seems to be the only portion involved, since the effects of total section are no greater than those of section of the rostral half.

Section of the anterior commissure of an otherwise intact monkey has no perceptible effect on motor behavior. However, in an animal lacking the callosum, but functionally recovered, anterior commissure section brings about a return of the callosal syndrome. If, in addition, area 4 has been destroyed bilaterally, there is no appreciable recovery, although if the motor cortex is intact, compensation again takes place. [This study has been supported in part by a grant from the John and Mary Markle Foundation.]

Temperature gradients in men exposed to cold E F ADOLPH and (by invitation) G W MOLNAR. *Dept of Physiology, School of Medicine and Dentistry, Univ of Rochester, Rochester, N Y* Temperature differences between deep tissues and body surface are maintained even in the presence of large heat flows. How large may they steadily be in the cold? Men were exposed outdoors in shorts for periods of 1½ to 4 hours. Rectal temperatures never fell below 35.9°C. Surface temperatures, read at ten points with unshielded thermojunctions, were nearly steady after ½ hours of exposure, their mean might fall to only 14.0°C when the air temperature was 1°C. Foot temperatures were usually within 3 Centigrade degrees of the dry-bulb temperatures. Gradients of 17 Centigrade degrees could exist in the trunk region.

The steep gradients were maintained by the heat production of shivering, which sometimes was four to five times resting. The rates of heat production, as measured by oxygen consumptions in closed circuit, were roughly inverse to air temperatures below 18°C or of mean surface temperatures below 25°C. About 8 Calories/hour were produced for each Centigrade degree added to the gradient. In the first hour of exposure, heat was unstored in amounts, as estimated roughly from tissue cooling,

almost equal to the heat production. Thereafter production was not further accelerated.

By the device of using its outer shell as insulation for the deep tissues, the human body maintains large temperature differences for as long a time as heat can be produced at fatiguing rates. [Work done under contract with the Office of Scientific Research and Development.]

The ability of anesthetized human subjects to breathe against continuous pressure SHANNON C ALLEN and A P GAGGE. *Aero Medical Lab, Air Technical Service Command, Wright Field, Dayton, Ohio* The standardization of pressure breathing oxygen equipment for use in AAF aircraft at altitudes above 37,000 feet raised the question as to whether an unconscious man such as an aircrew member suffering from wounds would continue to breathe against continuous pressure.

As an approach to the problem one young husky volunteer subject and one elderly emaciated clinical patient were put under light surgical anesthesia with sodium pentothal administered intravenously. Both subjects were able to breathe against eight inches continuous water pressure without difficulty. In the older subject both tidal air and minute volume were reduced to 65 per cent and 70 per cent, respectively, of control level despite an increase from 20 to 22 in respiratory rate. In the younger subject both tidal air and minute volume were depressed at four and six inches but rose again to 83 and 100 per cent of control, respectively, at eight inches with respiratory rate increased from 20 to 24. In contrast in an anesthetized control experiment the average of five subjects showed a continuous increase in both tidal air and minute volume and little change in heart rate.

Although the small number of subjects makes it unwise to draw conclusions as to the reaction of aircrews who are unconscious (from wounds or shock) it can be said that it is unlikely that pressure breathing *per se* will cause cessation of respiration in unconscious subjects.

Effect of destroying three localized temporal lobe areas on correct conditioned differential responses of the dog's foreleg from general cutaneous stimuli WILLIAM F ALLEN. *Dept of Anatomy, Univ of Oregon Medical School, Portland* Dogs previously operated for a sound problem and others were used. The cortical areas eliminated were A, B and C (fig 1, Amer J Physiol Vol 144). Two sets of general cutaneous analysers were

used In one set the back were stroked once per second with and against the grain and in the other it was stroked with the grain, once and three times per second

Results Destruction of areas A or B or both A and B caused little or no effect on the appearance of correct conditioned differential responses with either set of tests Deletion of areas B and C or A, B and C abolished for over 1100 tests the ability to make correct responses with both sets of tests Destruction of area C disrupted somewhere the usual mechanism for making these correct conditioned differential responses and it required several hundred tests before new and un-erring circuits were established None of the bilateral lesions affected the positive conditioned reflexes and one side lesions produced no effect on either set of tests

With the general cutaneous tests, deletion of area C was equivalent to destruction of areas A and B with the previous auditory tests Total elimination of correct responses with general cutaneous stimuli followed destruction of areas B and C, while like effects from auditory stimuli required destruction of areas A, B and C Inability to make these correct responses after the lesions was characterized by failure to inhibit correctly, due presumably to injury to the association circuits and/or the neighboring inhibitory bands

A comparison of the clinical antimalarial properties and toxicity of several 8-amino quinolines using plasmochin as a standard of references ALF ALVING, LILLIAN EICHELBERGER, (by invitation), BRANCH CRAIGE, JR (by invitation), RALPH JONES, JR (by invitation), THEODORE PULLMAN (by invitation) AND C MERRILL WHORTON (by invitation) *The Malarial Research Unit, Dept of Medicine, The Univ of Chicago* A group of 8-amino quinolines with varying substituents on the quinoline ring, and on the side chain in the 8-position, have been systematically Prison inmate volunteers who have submitted to sporozoite-induced (Chesson) vivax malaria have served as subjects Using techniques previously standardized in a study of plasmochin and quinine, it has been possible to assay the clinical antimalarial properties and the toxicity of these compounds quickly

Compounds illustrating the usefulness of this "screening" technique will be discussed One of the compounds studied, SN 13,276, although considerably less toxic than plasmochin, possesses similar antimalarial properties [*Work done under contract with the Office of Scientific Research and Development*]

Clinical experience with hemoglobin-saline solutions WILLIAM R AMBERSON, C MARTIN RHODE (by invitation) AND JOYE J JENNINGS (by invitation) *Dept of Physiology, School of Medicine, Univ of Maryland, Baltimore, Md*

Hemoglobin saline solutions (Hb = 10 to 12 gm %) have been prepared which are usually non-pyrogenic when injected intravenously into clinical cases Most patients exhibit a rise in blood pressure persisting for several hours, associated with bradycardia In one case of hypertension, however, blood pressure fell moderately after infusion Most patients have tolerated the solution well, with only occasional symptoms of distress

In four cases of post-hemorrhagic anemia definite hematopoietic stimulation has been observed after administration of hemoglobin-saline, with reticulocytosis and increased hematocrit values Best results have been obtained by repeated injections of small volumes (100 to 200 cc) over a number of days

In one case of massive hemorrhage after childbirth infusions of plasma and whole blood failed to raise blood pressure above shock levels Administration of hemoglobin-saline caused a rapid rise in blood pressure and return of consciousness within ten minutes A total of 2300 cc was given Shock did not recur Renal failure, however, developed, with uremia, death from heart block occurred on the ninth day

In two other cases signs of renal impairment appeared after infusion of hemoglobin-saline, but function later returned to normal In all other cases urea clearance measurements gave no definite evidence of renal impairment

The series of 12 cases is not extensive enough to establish a therapeutic value for such solutions They do, however, present several favorable indications which seem to justify further clinical tests with more carefully prepared solutions

Studies on the perfusion of the isolated pancreas factors influencing insulin production EVELYN ANDERSON, JOSEPH A LONG (by invitation) AND ERNA LINDNER (by invitation) *Inst of Experimental Biology and Division of Medicine, Univ of California, Berkeley and San Francisco* (Read by title) With the use of a small perfusion pump circulation was maintained in the isolated rat pancreas (including also the stomach, duodenum and mesentery) for two hours Evidence of a living organ was demonstrated by its utilization of oxygen and glucose and by the stimulation of insulin production when the glucose in the blood perfusate was raised to 300 mg per cent The assay of insulin in the blood perfusate was done on demedullated, alloxan-treated, hypophysectomized rats Three cc of blood perfusate was injected intravenously and the change in blood sugar level observed during a 30 minute period

Studies are being made to determine what conditions besides hyperglycemia will stimulate insulin production directly A purified growth hormone preparation added to the perfusate did not stimulate the pancreas to produce insulin

The activation of bacterial viruses by aromatic

amino acids THOMAS F ANDERSON (introduced by D W Bronk) *Johnson Foundation, Univ of Pennsylvania, Philadelphia* Five out of a set of seven bacterial viruses under study will attach their host, strain B of *E coli*, in a synthetic ammonium lactate medium. The remaining two viruses in the synthetic medium show $\frac{1}{1000}$ the activity they exhibit in Difco nutrient broth. These viruses, T4 and T6, require at least 1 microgram of *l*-tryptophane/cc, 100 micrograms of *dl*-phenylalanine/cc, or 1000 micrograms of *l*-tyrosine/cc in the medium before they are fully active on the host. Further experiments have shown that these viruses cannot attach themselves to the host's cell wall without a suitable co-factor. Once the virus is adsorbed on the host it is able to multiply and lyse the host cell even in the absence of a co-factor (Anderson, *J Cell and Comp Physiol*).

Recently it has been found that T4 and T6 viruses are not activated by *d*-tryptophane, but are activated by many synthetic aromatic *dl* α -amino acids.

The viruses, rather than the bacteria, are activated by the co-factors, for on exposure to *l*-tryptophane they gain activity. Also, after removal of the tryptophane, they lose activity at a measurable rate. No effect of exposure of the host alone to *l*-tryptophane has been detected.

These results suggest that the co factors may alter the virus surfaces to make them conform to receptor spots on the host surface—or the co factors may even act as coenzymes, enabling the viruses to penetrate into the host when they encounter its cell wall.

Riboflavin metabolism after trauma and during convalescence in man W A ANDREAE (by invitation), VICTOR SCHENKER (by invitation) AND J S L BROWNE *McGill Univ Clinic, Royal Victoria Hospital, Montreal, Canada* The 24-hour urinary excretion of riboflavin was followed in 23 patients who had suffered fracture and burn injuries and whose daily intake level of this vitamin was kept constant at 50 mg by supplements of crystalline riboflavin. Whereas about one half the ingested riboflavin was retained at this intake level in health, patients after acute injuries characteristically showed a marked retention during the initial 3 to 5 days after injury. This state was followed by a period of similar duration when there occurred an increased riboflavin loss as shown by the excretion rate. After about ten days following the injury, the riboflavin balance returned to normal. This would suggest that the vitamin retained during the first period was not utilized or destroyed, but was stored in some way and subsequently released. Observations made on these patients during convalescence demonstrated a retention of riboflavin coincident with a retention of nitrogen. This correlation was statistically

analyzed and found to be highly significant so that for each gram of nitrogen retained, 0.30 mg of riboflavin was retained over and above the normal baseline.

The respiration of nerves and arteries of adrenalectomized rats CLIFFORD A ANGERER *Dept of Physiology, The Ohio State Univ, Columbus* To date, 84 experiments have been performed on the sciatic nerves of rats. An experiment represents running samples from a tissue pool in triplicate or quadruplicate. This represents a study of slightly more than 350 rats (80–120 gms, males). In recording the Q_{O_2} values for the nerves by Penn's differential volumeters, the results show that there is no decrease in respiration of the sciatic nerves of adrenalectomized rats as compared with the controls. There is a decrease of ca 29% in Q_{O_2} values of the descending aorta of adrenalectomized rats as compared with the controls.

Human centrifuge operation E J BALDES AND A N PORTER (by invitation) *Acceleration lab, Mayo Aero Medical Unit, Rochester, Minn* (Motion picture) The motion picture illustrates the principles and the mechanism involved in the operation of the human centrifuge at the Acceleration Laboratory, Mayo Aero Medical Unit. The centrifuge has two essential parts: a superstructure or carriage and a pair of rotating flywheels. The superstructure and the flywheels rotate in the horizontal plane about a common axis. The flywheels are driven by a Chrysler automobile motor powered by natural gas. The rotating flywheels, which weigh approximately 20 tons apiece, provide the energy for the rapid development of accelerative forces in the superstructure. The superstructure is set in motion by clutching to the flywheels and is brought to a standstill by declutching from the flywheels and braking on a rigid foundation. The speed of rotation of the superstructure is controlled by the clutch and the speed of the rotating flywheels. With this control the exact acceleration desired may be delivered rapidly or slowly for any required period in the superstructure. At one end of the superstructure is a gondola or cockpit so suspended that it swings outward when the centrifuge is in motion and in which the subject or pilot may sit, stand or lie. The other end of the superstructure is closed by a solid partition, sufficient space being provided for a variety of experiments under various accelerations. [Work done under contracts with (1) United States Army Air Forces, Wright Field, Dayton, Ohio, and (2) the Office of Scientific Research and Development, National Research Council, Washington, D C].

The effect of the continuous administration of p-aminopropiophenone on the blood in man J H BANNON, JR, D J W ESCHER AND M BEVELANDER (introduced by Homer W Smith) *Dept of Physiology, New York Univ College of Medicine* Oral administration of p-aminopropio-

phenone at four-hour intervals for periods from 14 to 30 days in doses of 0.7 to 1.6 mg/kg consistently produced methemoglobinemia of 5-25%, 8-15% remaining after four hours

Evidence of hemolysis was present during ten courses of administration in 6 subjects, as indicated by decrease of 0.5 million or greater in erythrocytes, 0.5 gms or more in hemoglobin and lowering of the erythrocyte hematocrit by the 4th to 6th day of medication. These changes progressed with total decrease of 2.5 million erythrocytes, 2.4-5.8 gms hemoglobin and 8.2-29% in erythrocyte hematocrit. Reticulocyte increase occurred on the 5th to 8th day, rising to a maximum of 5.8 to 11.2% by the 17th day.

That these alterations were primarily due to hemolysis was indicated by icterus of skin and conjunctiva, rise in serum bilirubin of both indirect and direct types by the 5th day, and a concomitant increase of fecal and urinary urobilinogen. Despite the withdrawal of large blood samples during drug administration and during control periods, return toward normal blood and serum values followed cessation of the drug.

A chemical relation between p-aminopropiophenone and substances of general therapeutic use (sulfonamides, acetanilid, phenylhydrazine) calls attention to a possible relation in the mechanism of hemolysis.

Absence of dinitro-cresol effect in thiouracil-treated rats S. B. BARKER, *Dept of Physiology, State Univ of Iowa, Iowa City*. It has been shown that rats rendered hypothyroid by thiouracil feeding exhibit an essentially normal elevation of BMR following administration of desiccated thyroid substance. It was thought of interest to study the metabolic response of thiouracil-treated rats to dinitro-o-cresol as another stimulant of oxygen consumption.

As untreated controls, 12 male and 4 female rats gave an average increase of 37.5 cc O₂/100 gm body wt/hr, or 37.9% over the basal rate of 98.9, immediately following the intraperitoneal injection of 10 mg of 3, 5 dinitro-o-cresol/kg body wt.

Ten male and 4 female rats treated with thiouracil for 79 to 105 days gave an average increase of 2.2 cc O₂/100 gm/hr, or 2.6% over the basal of 85.1, following the same dose of dinitro-o-cresol.

The apparently normal response of thiouracil-treated rats to thyroid substance stands in contrast to the greatly decreased response of these animals to dinitro-o-cresol. This result suggests that dinitro-l-cresol either operates through the thyroid gland or requires thyroid hormone for its extra-thyroid activity. The wide disparity in time curves for the dinitro-o-cresol and thyroid effects on metabolic rate is contradictory to the first explanation.

A method of scoring a patient's electroencephal-

ogram in deep breathing giving a cerebral hyperventilation index T. C. BARNES AND M. D. AMOROSO (by invitation) *Dept of Physiology, Hahnemann Medical College and Hospital of Philadelphia* (Read by title). Previous reports (Barnes, Federation Proceedings 4, 5, 1945) have shown that abnormal waves appear in EEG in hyperventilation when the blood sugar is low, vital capacity adequate to produce apnea, the pulse rises and vasoconstriction is sufficient to produce a fall in skin temperature of the hands. We rate EEG in hyperventilation as follows: A slight slowing of the waves rates -3 to -6 depending on the degree of abnormality. Paroxysmal delta rates -8. Spike-and-dome waves get -10 to -15 depending on time to appear and the duration of the bursts. Blood sugar above 130 rates -4 and below 130, +4. An adequate vital capacity rates +2. A moderate rise in pulse gets +2 and a rise of 25 beats or more rates +4 (due to vigorous effort and inactive parasympathetic compensation described by Darrow). Good effort to ventilate rates +2 and moderate effort rates -2. Fall in skin temperature (Palm) rates +3 and rise -3. Physiological changes that produce abnormal waves in normals are rated plus and factors that protect EEG are minus. Unchanged variables rate zero. Average score was +5.00 ± 0.80 for 27 normal students and -4.58 ± 1.40 for 27 patients with history of seizures. Worse possible score is -28 (one petit mal case rated -15). Highest possible score is +17 (one army medical student attained +15).

It is useless to take routine EEG without study of all related physiological variables of the organism as a whole. Abnormal waves in hyperventilation are due to destruction of acetylcholine by alkalosis. We assume that brain potentials are phaseboundary potentials produced by acetylcholine (Barnes and Beutner *J Exp Med Surg* 3: 325, 1945).

The effect of healing agents on the wound potential of human skin T. C. BARNES *Depts of Pharmacology and Physiology, Hahnemann Medical College and Hospital of Philadelphia*. Measurement of the positive wound potential of experimental abrasions on the fingers provides objective criteria for healing rate (Barnes, *Am J Surgery*, 69: 82, 1945). Fractions of liver oil were found to give different healing indices. Each fraction was equivalent to 10% crude oil in a lanolin-petrolatum base containing 10% yeast derivative and 1/20,000 phenyl mercuric nitrate. Saponifiable oil gave healing index of $2.93 \pm 0.16\%$ wound potential lost per hour compared with $2.40 \pm 0.18\%$ for non-saponifiable (32 abrasions on alternate fingers). Crude oil gave healing index of $2.34 \pm 0.18\%$ compared with $2.13 \pm 0.23\%$ for petrolatum controls on alternate fingers of same hand. The results indicate that liver oil preparations have definite healing action and that the saponifiable fraction is best.

The healing index for 1% chlorophyll (in saline, petrolatum or synthetic phenolic resin) was $2.43 \pm 0.37\%$ compared with $1.13 \pm 0.27\%$ for controls of vehicles alone (40 lesions)

Embryonic extract was without healing action contrary results reported by Goldberg (Am Rev Soviet Med 2 225 1945) 50% macerated dog embryo in petrolatum with 2% chloretone and 1 40,000 metaphen gave healing index of $1.36 \pm 0.30\%$ compared with $1.94 \pm 0.50\%$ for vehicle controls (24 lesions)

Recent results show that the index finger has the lowest potential and heals fastest, so ointments must be tried on different fingers. A long salt bridge may be used to measure the potential of a wound on any part of the body. We are now making a series of abrasions along the arm but this skin heals more slowly than the fingers.

Electrical activity of acetylcholine compared with choline, acetate, phosphate, potassium and other substances associated with nerve activity. T. C. BARNES AND R. BEUTNER, *Depts of Physiology and Pharmacology The Hahnemann Medical College and Hospital of Philadelphia* (Read by title). Acetylcholine is the only substance in nerve capable of producing the spike potential. On an interface between 0.9% NaCl and nitrobenzene 0.2% KCl has no detectable electrical effect, 0.1% tetramethylammonium iodide has no effect, but 0.1% acetylcholine establishes a potential of 30 millivolts negative. 0.2% choline chloride produces 5 millivolts negative and 0.1% sodium acetate gives 7 millivolts positive. The latter two potentials may be the negative and positive afterpotentials which follow the spike in living nerve. Recent work has linked acetylcholine metabolism with phosphorus compounds. 0.05% dibasic sodium phosphate establishes a positive phase boundary potential of 7 millivolts on guaiacol which suggests that one of the two positive afterpotentials in nerve may be phosphate effects.

We have previously emphasized the importance of the type of oil in the nerve membrane. For example, triglycerides react like adrenergic nerves in that they establish potentials with sympathetic drugs but not with acetylcholine. Another example is tetramethylammonium iodide of which 0.1% gives no potential on nitrobenzene but 20 millivolts negativity on 5% cholesterol in guaiacol.

The experiments show that the old Bernstein theory of polarization by inorganic ions such as K is untenable. Acetylcholine is the nerve substance that gives negativity of sufficient magnitude. There remains the possibility of small after potentials produced by other organic substances like phosphate. [Aided by a grant from the American Philosophical Society.]

Bioelectrical studies of fatigue. I. Recovery of fatigued polarized muscle by reversal of the

poles of the galvanic current. T. C. BARNES AND I. MAUER (by invitation) *Dept of Physiology, Hahnemann Medical College and Hospital of Philadelphia* (Read by title). A time-honored experiment (Biedermann, *Electrophysiology* 1 292, 1896; Schaefer, *Elektrophysiologie* 1 70, 1944) shows that an excised frog muscle stimulated by a series of galvanic stimuli becomes fatigued but on reversing the direction of the current recovery occurs—the Wendungseffekt of Scheminzy (Pflüger's Arch 231 192, 1932). The results are so easily obtained that it makes a reliable experiment for the students' laboratory. We use Ag-AgCl or Zn-ZnSO₄ boot electrodes, one dry cell and stimulation twice per sec with current reversal every 20 secs. Gastrocnemii are taken from frogs curarized with 1 mg of intocostin. It seems unlikely that it is possible to add anything new to this simple muscle experiment but most of our kymograph records show better recovery when the cathode is situated proximal to the anode (nearer the origin of the muscle). This orientation may be related to the recent finding of Pollock (J Mt Sinai Hosp 9 688, 1942) that the muscle becomes negative at the proximal end when stimulated. The greater response with proximal cathode cannot be explained by Biedermann's claim that the thin end of a muscle (sartorius) increases current density. The pinnate structure of the gastrocnemius (Beritoff, Pflüger's Arch 209 763, 1925) might account for the greater effect of proximal cathode with both electrodes near the insertion. We are unable to explain why every second pole change gives better recovery with a transverse current (tips of boot electrodes on opposite sides of belly of muscle or AgCl wires placed along the entire length on each side).

Biological studies of fatigue. II. Students' electroencephalograms taken at 8 AM and 5 PM. T. C. BARNES AND H. BRIEGER (by invitation) *Departments of Physiology and Industrial Hygiene, Hahnemann Medical College and Hospital of Philadelphia* (Read by title). Gruttner (Arch Psychiat Nervenkr, 111 652, 1940) claimed that severe fatigue destroys the regular alpha rhythm of EEG. We found that the EEG of students taken before and after a routine day of classes showed little evidence of fatigue. Of 27 students, 4 had no alpha at any time, 12 showed no change of alpha, in 4 alpha increased and only 7 lost per cent time alpha during the day. Statistical analysis by Dr O. W. Richards, American Optical Co., revealed that the probability is only 0.171 or once in 4 sets of 23 students the distribution of 7, 4, 12 would occur. The mean per cent time alpha was 51.1 ± 3.96 in AM and 52.5 ± 2.70 in PM. White blood cell counts showed in general the usual afternoon rise. Blood sugar, skin temperature, vital capacity, and pulse rate in hyperventilation were

correlated with delta waves. The mean hyperventilation index (see Barnes, These Proceedings) was $+2.74 \pm 0.79$ in AM and $+4.00 \pm 0.80$ in PM. We conclude that the EEG shows no change or a slight decrease in alpha at 5 PM and the susceptibility of the brain to apnea is higher in the AM.

One student fell asleep during the PM test and showed immediate slow sleep waves. One student had severe petit mal waves in hyperventilation in both AM and PM. These abnormal waves were abolished by amyl nitrite showing the importance of cerebral vasoconstriction in EEG.

Eye opening, mental arithmetic and visualization with eyes closed blocked alpha to about the same degree AM and PM.

Electroencephalography of infants under pentothal anesthesia. T. C. BARNES, H. S. RUTH (by invitation) and E. K. HULTZMAN (by invitation), *Depts. of Physiology and Anesthesia, Hahnemann Medical College and Hospital of Philadelphia* (Read by title). It is very difficult to secure an electroencephalogram of babies owing to artefacts produced by muscular movements of the face and limbs. The EEG of the frontal lobes especially is obscured by eye movements. We have found that rectal pentothal 0.015 to 0.020 gram per pound gives anesthesia satisfactory for electroencephalography. First an EEG is taken before anesthesia to aid in the recognition of the typical pentothal waves. Anesthetization takes 7 to 40 minutes (one baby weighing 28 pounds required 0.9 gram of pentothal). Fast high voltage waves typical for pentothal (15 per second 100 microvolts) are seen for the first hour or more and these are replaced by normal slow sleep waves. By careful study of the record before and after pentothal it is possible to detect the absence of regular rhythms in cerebral agenesis, the presence of epileptic waves and traumatic waves especially if the trauma is lateralized. The fast pentothal waves (described by Katzenelbogen and by Brazier) are easily recognized from the normal slow waves of infants. The pentothal waves are widespread in contrast to abnormal waves from localized lesions. The frontal lobes show more of the pentothal waves but this localization is not as marked as in adults. It is remarkable that the very slow 2-4 per second waves of one year old infants can be accelerated to 15 per second by pentothal showing that a neuronal structure is present capable of transmitting waves even faster than the normal adult rhythm of 10 per second.

Intrapulmonary mixing curves and the detection of abnormal ventilation. J. B. BATEMAN, *Mayo Aero Medical Unit, Rochester, Minnesota*. The time course of lung nitrogen elimination during unforced breathing of pure oxygen is determined by several variables, notably (1) mid-capacity ("functional residual air"), (2) respiratory dead space, (3) tidal volume, (4) rate of nitrogen transfer from blood to alveolar gas, (5) uniformity of dis-

tribution of tidal air. When simplifying assumptions are made the course of removal of nitrogen from a single perfect mixing chamber can be calculated as a function of (1), (2), (3) and (4).

An open circuit method has been devised for measuring the course of expiration of nitrogen during inhalation of pure oxygen. Values of (1), (2) and (4) can nearly always be assigned to give a theoretical curve that will fit the experimental data, known changes in tidal air or respiratory dead space displace the experimental points to the calculated extent.

The curve which fits the experimental data provides, we believe, a reliable value for the mid-capacity. The value of the apparent dead space embodies both the respiratory dead space and the effect of unequal distribution of tidal air, or of imperfect mixing brought about by other means. It may therefore be regarded as an index to the effectiveness of the lung as a mixing chamber, and data have been collected on normal persons and patients with pulmonary lesions (emphysema, bronchiectasis, bronchial obstruction) which provide support for this point of view.

Chronic motor disability resulting from repeated exposure to oxygen at high pressure. JOHN W. BEAN and ERNEST C. SIEFRIED (by invitation), *Dept. of Physiol. Univ. of Mich. Ann Arbor*, (Motion Picture). Albino rats about 3 months old were exposed to O_2 at 65 pounds pressure (gauge) for from 10 to 25 mins. 2 to 4 times per day until a desired degree of residual disability was induced. In so far as possible convulsive attacks were avoided. CO_2 was absorbed from the chamber and temp. maintained at about $24^\circ C$. Decompression was such as to avoid any possibility of bubble formation.

Reactions manifest on the animal's removal to room air after single exposures varied widely in type and severity, symptomatic recovery from these acute reactions usually occurred within a few minutes or hours. But with repeated exposures, commonly as few as 5 or 6, but rarely after a single exposure, motor disabilities associated with chronic spastic paralyzes involving the limbs and body musculature were induced. Some symptomatic recovery from these chronic changes was evident but the persistence of very pronounced disability for periods as long as 18 months when the animals were sacrificed indicate these chronic changes are permanent.

Chicks (8 days old) exposed to O_2 at 90 and 65 pounds in a similar manner over a period of days were affected in like manner, disability thus induced persisted into adult life. The nature of this dysfunction is highly suggestive of permanent injury in the C.N.S. by the high O_2 pressure and finds confirmation in histological studies. Some of the reactions also suggest visual disability.

The Shear tumor necrotizing bacterial poly-

saccharide as a pyrogen LYLE V BECK *Dept of Physiology, Hahnemann Medical College, Philadelphia, Pa* ¹ The highly purified tumor necrotizing polysaccharide secured from *Serratia marcescens* by M J Shear and co workers is extremely potent as a pyrogen when given intravenously to rabbits ² 0.005 micrograms per kg produced a measurable rise in rectal temperature. A maximum rise of 2 to 3° C was produced by as little as 0.50 micrograms per kg. Further increases in amount of polysaccharide administered did not bring about any further increase in the fever reaction. Rabbits receiving lethal and semi-lethal amounts of the polysaccharide (20 to 100 micrograms per kg) were likely to show a weak fever reaction. Rabbits showing a weak fever reaction were very likely to die within 24 hours after administration of the polysaccharide.

The polysaccharide not only induced a rise in rectal temperature but also an extremely rapid and extensive decrease in ear temperature. Skin temperatures on the back and abdomen ran parallel with the rectal temperature.

Rabbits tied down in the copper trough of an animal table failed to show increases in rectal temperature, although the ear temperatures became and remained low for hours. The fever reaction was not much affected by tying rabbits down on cardboard.

The following amounts of various drugs given by stomach tube were required to markedly counteract the fever reaction: antipyrine, 300 mg per kg, isopropyl antipyrine, 150 mg per kg, acetylsalicylic acid, 500 mg per kg. Dial, 40 mg per kg, intravenously, was also quite effective.

Study of learning and memory in guinea pigs suffering brain concussion. R F BECKER, R A GROAT and W F WINDLE *Department of Anatomy and Inst of Neurology, Northwestern Univ Medical School, Chicago*. Two groups of guinea pigs were trained to perfection on a simple maze in which the correct exit always lay behind the last of two blind alleys. Animals learned a right and left hand pattern and then one in which the blinds alternated in a chance sequence. Criterion of learning was ability to run 10 errorless trials in succession. In Group I, subgroups were taught the problem 6, 30 and 90 days after concussion. Untreated controls were provided for comparison. After initial learning the subgroups were retested on the chance alternation pattern at various intervals of time. Group II animals were taught the problem first. Subgroups were retested 6, 30 and 90 days later and then received concussions. A second retest followed 6, 30 or 90 days after concussion.

Animals with concussion were unable to effect

a systematic solution of the problem during the initial stages of learning. Their early running was purely random and disoriented. They made and repeated many more errors than did the controls. In later stages of learning they performed as well as controls. This disorientation was not as marked in animals first meeting the problem 90 days after concussion.

All experimental animals suffered marked retentive loss and required extensive retraining in retests regardless whether the problem was learned before or after concussion. Repeated retesting did not improve retention. Controls were letter-perfect even 90 days after initial learning. [Work done under contract, sponsored by CMR, between OSRD and Northwestern Univ.]

Continuous blood oxygen saturation in intravenous barbiturate anesthesia. VIVIAN G BEHRMANN (introduced by ROBERT GESELL) *Dept of Labys, Henry Ford Hospital, Detroit, Michigan*.

Anoxia is a hazard often encountered in anesthesia, which is not given sufficient attention. The current widespread usage of intravenous anesthesia coupled with the dearth of adequate data on the blood oxygen values prompted this study. In the numerous clinical reports on the usage of the short-acting barbiturates, namely Evipal and Pentothal, one finds that oxygen inhalation is advised to prevent respiratory depression. In short operations, it is not feasible to determine oxygen saturation of the blood since an arterial puncture is involved and the accepted method is time-consuming. Therefore, a photoelectric method for the continuous recording of oxygen saturation of the blood affords a useful instrument for obtaining data under short-time anesthetics.

Continuous blood oxygen saturation curves, with simultaneous records of respiration and blood pressure were obtained under intravenous administrations of barbiturates to normal dogs. A series of patients undergoing operations were also studied. The dosage of barbiturate was altered in the experimental animals so as to produce light, moderately deep, and deep anesthesia. The depth of anesthesia was noted frequently through the state of the corneal and lid reflexes. The oxygen saturation curves were checked at intervals using Van Slyke's manometric method for oxygen saturation of arterial blood.

Factors maintaining heat balance of the clothed man at different grades of activity in the cold. H S BELDING, H D RUSSELL (by invitation) and R C DARLING *Fatigue Lab, Harvard Univ, Boston, Massachusetts*. Men have been exposed for two hour periods at 0°F in a standard arctic uniform while seated, standing, walking or climbing. The data gathered have permitted calculation of energy production and body heat debt, as well as energy loss by evaporation from the lungs and skin,

¹ Supported by grant from International Cancer Research Foundation.

² Nat. Cancer Institute 4: 81-122 (1943).

by warming the inspired air, by work, and by convection and radiation through the clothing

At all levels of activity most of the heat was lost by convection and radiation, the resistance to heat flow by these avenues was a function of the amount of surface area exposed as well as of the speed and extent of the body movements, it was three times as great during sitting as during fast walking

The calculation of body heat loss by sweating was complicated by the fact that most of the sweat remained in the clothing. However, since evidence exists that most of this had been evaporated at the skin and later recondensed it was possible by making reasonable assumptions to calculate the effective rewarming of the body resulting from recondensation of the moisture in the various layers, then the heat of vaporization of all of the sweat minus the effective recondensation equalled the body heat loss by sweating. It was found that the net efficiency of the sweat for body cooling never exceeded 60 per cent and only attained this figure when sweating was moderate. The inefficiency of this method of cooling was compensated for by an increase in the total amount of secretion.

The origin of the spike potential in nerve R. BEUTNER and T. C. BARNES *Dept of Pharmacology and Physiology, The Hahnemann Medical College and Hospital of Philadelphia*. Electric phase boundary potentials between a lipid and saline *in vitro* are made negative by traces of acetylcholine, suggesting relationship between the "negative variation" of nerve and acetylcholine generation. However, the rapid disappearance of the negative variation cannot be explained through decomposition of acetylcholine by esterase, since inhibition of esterase by eserine has no effect. Even external application of acetylcholine has no effect on the nerve. The generation of acetylcholine must therefore take place in the lipid itself of the membrane where it is protected against the esterase (W. Feldberg, 1945).

We assume that acetylcholine is first generated on one side in the lipid of a membrane of the nerve, thus originating the up-stroke of the spike potential. The down-stroke would occur if acetylcholine reaches its opposite side. Experiments showed disappearance of *e m f* if acetylcholine is on both sides of oil layer.

Additional experiments were done on oil layers of varying thickness. If the layer is about 1 mm thick the negativity produced by 0.05% of acetylcholine lasts for hours without perceptible change, or it even rises. If the oil layer is about 0.1 mm thick so as to appear as a film the *e m f* of the oil cell drops from an initial value of 34 millivolts to 4 millivolts in 5½ hours. Assuming the cell membrane to be about 1μ thick or less we can understand that the drop of potential occurs in a few σ

[Aided by a grant from the American Philosophical Society]

The mechanism of estrogen induced changes in dominance-subordination relationships in the female chimpanzee HERBERT G. BIRCH (by invitation) and GEORGE CLARK *Yerkes Labs of Primate Biology, Orange Park, Florida*. In both intact and castrate-female chimpanzees rise in estrogen level is accompanied by increase in social dominance. In the male chimpanzee, however, a rise in estrogen level is followed by a decrease in dominance. There are two possible explanations of the sex difference in the effect of estrogens. 1. Different integrative patterns in the central nervous system are postulated. 2. The presence of the genital swelling, which occurs only in the female, in some way modifies her dominance.

A test of the influence of the genital swelling is made possible by altering the temporal sequence of administration of estrogen and progesterone in combination. Swelling or non-swelling can be attained at the same blood concentration of the hormones, depending upon time relations of administration. With such control of one female castrate in a food-competition situation, the level of dominance varied directly as the size of the genital swelling and did not correlate with the blood level of estrogen. The estrogen induced dominance of the female is thus to be ascribed to the production of the genital swelling and the resultant increased irritability of the animal.

Oxygen and CO₂ dissociation curves of the blood of the Atlantic salmon *Salmo salar salar* Linnaeus acclimated to winter temperatures. EDGAR C. BLACK and VIRGINIA S. BLACK (by invitation) *Dept of Physiology, Dalhousie Univ, Halifax, Nova Scotia, Canada*. Oxygen and CO₂ dissociation curves were constructed at 5°C for the blood of the Atlantic salmon, *Salmo salar salar* Linnaeus, acclimated to winter temperatures (2° to 6°C). The salmon left the sea early in October, 1945 and had been in cold fresh river water for 6 to 10 weeks before they were used. The fish weighed from 2 to 10 pounds. Both sexes were used. Oxygen dissociation curves constructed at 5°C and pCO₂ 0-2, 10 and 40 mm indicate that the oxygen combining power of salmon blood is sensitive to CO₂, although not unusually so for fish blood. The tensions of oxygen at unloading (half saturation) were 7, 32 and 35 mm at CO₂ pressures of 0-2, 10 and 40 mm respectively. The CO₂ dissociation curves show a typical Haldane effect and also indicate that maximum buffering occurred between pCO₂ 0 and 10 mm. In 3 estimations, the CO₂ venous tensions of blood taken from the heart were 3, 6 and 6 mm while the corresponding oxygen tensions were 14, 8 and 16 mm. The average oxygen capacity for 17 fish was 11.5 volumes per cent while the average red cell volume was 28 per cent.

These data are discussed in relation to the physiology and ecology of the Atlantic salmon [This work was supported by a grant from the National Research Council of Canada]

Photolytic lipids from visual pigments ALFRED F BLISS (introduced by H E Humwich) *Dept of Physiology and Pharmacology, Albany Medical College, Union Univ, Albany, New York* Rhodopsin, the light sensitive pigment from the retinal rods and the basis of night vision, is a conjugated protein which breaks down in the light, releasing a yellow vitamin A derivative, retinene (Wald, *J Gen Physiol*, 1935)

In 1937, the first step in the chemistry of daylight vision was taken by Wald who reported the extraction from chicken retinas of a red-sensitive cone pigment, iodopsin. The present author has studied the photochemical properties of iodopsin, finding it to possess in even greater degree the protein like lability of rhodopsin. The spectral sensitivity of dissolved iodopsin roughly paralleled Hecht's computation of the sensitivity of the human cones and showed a maximum at 570 mμ in the yellow-green.

New experiments have furnished information concerning the photoproducts of bleached iodopsin. The experimental material consisted of a powder obtained from chick or frog retinas frozen-dried in vacuo. The powder was moistened, bleached and extracted with $\frac{1}{2}$ per cent alcoholic petroleum ether. The lipids released by iodopsin proved spectroscopically identical with those from rhodopsin in both the frog and chick and showed a maximum density at about 390 mμ in chloroform, indicative of retinene. A variable peak at about 470 mμ was likewise evident but declined rapidly, leading to a stable spectrum identical with that of retinene.

The labile intermediate may represent the "transient orange" or "indicator yellow" stage of bleaching rhodopsin (Lythgoe and Quilliam, *J Physiol*, 1938) and has not previously been observed in nonaqueous solutions.

Physiology of the rat at high altitudes F R BLOOD, (by invitation) and F E D'AMOUR, *Univ of Denver*. The rat survives the anoxia of 40,000 feet, (140 mm) for considerable periods. It is therefore a suitable animal in which to study the adaptations of physiologic function to anoxia. In this study we have determined the values of a number of respiratory and circulatory constants at a low altitude and at 40,000 feet. These values are as follows, (first figure, Denver, second figure, 40,000 feet)

Oxygen consumption 26.3 mg/kg/min, 11.3 mg/kg/min. Respiratory Quotient 76, 1.39. Respiration rate 55, 53. Pulmonary Ventilation 114 ml/min, 218 ml/min. Alveolar Carbon dioxide 40.2 mm, 11.7 mm. Alveolar oxygen 73.8 mm, 10.2 mm. Arterial carbon dioxide 37.2 v p c, 17.8

v p c. Arterial oxygen 18.6 v p c, 4.2 v p c. Venous carbon dioxide 47.3 v p c, 27.6 v p c. Venous oxygen 9.4 v p c, 1.2 v p c. Blood R Q 1.19, 2.86. Coeff of Utilization 49%, 70%. Systolic blood pressure 144 mm, 122 mm. Heart rate 310, 222. Body temperature 37.3°C, 34.1°C.

Inhibition of erythema of sunburn by large doses of ultraviolet radiation H F BLUM and W S TERUS (by invitation) *Naval Medical Research Inst, Bethesda, Md*. The erythema produced in human skin by moderate doses of ultraviolet radiation may be partially inhibited by large doses of the same radiation applied subsequently. As a result, an optimum dose for erythema may be found when a series of graded doses is given. However, total skin damage is not inhibited in the same way as erythema, the degree of desquamation and vesiculation increasing progressively with the dose regardless of the degree of erythema which precedes. The inhibition of erythema is due principally to the longer wavelengths of the erythema spectrum, which penetrate more deeply than the shorter. It is concluded that the inhibition is probably a direct effect of these longer wavelengths on the minute vessels of the papillary layer to which they penetrate, whereas the erythema is caused by a dilator substance elaborated by injured cells of the malpighian layer. The results of this study indicate that the erythema threshold, and the erythema spectrum are at best only rough measures of sunburn and if used uncritically may lead to erroneous conclusions.

Uric acid formation in the developing egg of the grasshopper *Melanoplus differentialis* JOSEPH HALL BODINE *Dept of Zoology, State Univ of Iowa, Iowa City* (Read by title). A detailed quantitative study has been made of the uric acid production during the complete development of the egg of the grasshopper, *Melanoplus differentialis*. A marked increase in uric acid occurs during the developmental phases ranging from 0.0004 mg per egg at the beginning and at hatching 0.035 mg per egg. During diapause or "block" no marked changes in the concentration of uric acid occur. The general trends of the uric acid curve are similar to those for the O₂ intake and CO₂ output of the egg. Evidence is presented suggesting that during active development of the egg approximately 6.6% of the energy utilized is obtained from protein.

Electrokymograms of heart border motion: principles of record interpretation BERT R BOONE (by invitation), FRED G GILICK (by invitation), W EDWARD CHAMBERLAIN (by invitation) and MORTON J OPPENHEIMER *Depts of Radiology and Physiology, Temple Univ School of Medicine, Philadelphia, Penna*. The electrokymograph, used with the fluoroscope, provides an apparatus specifically designed for the convenient recording of heart border motions in the intact human subject.

Various points on the borders of the cardiovascular silhouette have their own characteristic motions, atrial, ventricular, venous, arterial or combinations of two or more such motions. These motions may be characteristically altered in the presence of cardiovascular disease.

Röntgen kymography has been used for the study of heart border motion but has failed to satisfy all of the requirements. Röntgen kymograms are of small size and lack detail. (Their lack of definition precludes the effective use of magnification.) Röntgen kymograms are necessarily brief. Electro-kymograms are tracings with all of the amplitude and detail of the electrocardiogram and may be run continuously for as long as is feasible for an ordinary fluoroscopic study of the patient's heart. In fact, electrokymography of heart border motion is accomplished with a fluoroscopic x-ray beam of ordinary routine intensity.

The interpretation of electrokymograms of heart border motion is greatly facilitated by simultaneous recording of the carotid pulse, on the same strip of bromide paper, through the same aperture as is used for the string galvanometer of the electrokymograph. By such means we have been able to identify five to six distinct phases in the motion curve of the left ventricle. Distinct phases are also demonstrable in motion curves of other portions of the cardiovascular silhouette.

Electrokymograms of motion of left ventricular border are surprisingly like typical ventricular volume curves.

Röntgen kymographic studies of cardiac and respiratory movements (motion picture) W M BOOTHBY and H F HELMHOLZ, JR (by invitation) *Mayo Aero Medical Unit, Rochester, Minnesota*. The movements of the breathing heart are clearly shown. The change in axis during positive pressure breathing is demonstrable and probably accounts for the apparent decrease in diameter.

The respiratory movements, especially those of the diaphragm, are also clearly shown and the rising of the diaphragm with positive pressure breathing is definite.

The movements due to the contractions of the diaphragm are apparently not simultaneous in different parts and give the appearance of a sinus character.

The influence of the pericardium on effective venous pressure T E BOYD and JOHN M BROOKHART (by invitation) *Loyola Univ School of Medicine, Chicago*. Earlier workers have shown that the pericardium limits distension of the heart under certain conditions (vagal standstill, anoxia, barbiturate poisoning). We have used dogs under morphine-barbital anesthesia. A cannula was tied into the apex of the pericardium, enough air (5 to 15 cc) introduced to maintain patency of the cannula, and intrapericardial pressure (IPP) recorded differentially against intrathoracic pressure

(ITP) in a closed pneumothorax of minimal volume. Venous pressure (VP) from the right atrium was recorded differentially against ITP and against IPP.

The rise of VP produced by intravenous fluids is relatively large against ITP, much smaller against IPP. During cardiac standstill from vagal stimulation, VP measured against ITP rises steadily until the heartbeat is resumed, but measured against IPP it becomes stabilized very slightly above the initial level. After severe hemorrhage this difference tends to disappear, a small and gradual rise occurring with either method of recording. Respiratory variations of VP are approximately the same by either method.

Breathing air under sufficient positive pressure (10 to 15 mm Hg) causes a marked fall of arterial pressure. This effect is not associated with a fall of VP, whether measured against ITP or IPP. In positive pressure breathing, neither ITP nor IPP (recorded as described) gives an accurate base from which to estimate effective venous pressure (see Brookhart and Boyd, accompanying abstract).

Acid effects of Ammonium compounds CHARLES R BRASSFIELD, ELWOOD T HANSEN (by invitation) and ROBERT GESELL *Univ of Michigan*.

Saliva pH and arterial blood pH were followed continuously with glass electrodes in anesthetized dogs. Salivary flow, respiratory volume, chest and abdominal movements were also recorded. The submaxillary gland was stimulated in three ways: intravenous injection of pilocarpine, electrical stimulation of the Chorda Tympani nerve and intra-arterial injection of acetylcholine.

Unlike ammonium chloride, ammonium hydroxide and ammonium bicarbonate increase the pH of arterial blood but all these compounds markedly decrease the pH of saliva. Salivary flow is increased by these compounds with all three types of secretory stimulation. Ammonium hydroxide and ammonium bicarbonate produced similar respiratory changes to those obtained with eserine or ammonium chloride.

These results suggest that ammonium compounds exert an anticholinesterase effect by virtue of an increased intracellular acidity. However, the specific effects of the ammonium radical or of the relationship of internal to external pH are not excluded.

Effects of acceleratory forces and their amelioration S W BRITTON and C R FRENCH (by invitation) *Physiological Lab, Univ of Virginia Medical School, Charlottesville*. Within limits, rat responses to g forces are fairly uniform for the same g x t values. Female animals tolerated g better than males, while young animals showed less resistance. Resistance differences for many animal species were observed. Negative g was tolerated only about half as well as positive g.

Increased resistance was shown by animals which had been given several exposures over periods of days or months

Considerable protection was afforded by a simple belt placed around the abdomen or upper thighs. The effects of pressor and other substances were studied. Respiratory and circulatory changes (including ECG) under various g forces were observed. Marked effects were observed in a few instances on the central nervous system, chronic rigidity (decerebrate type) sometimes appeared. "Delta" brain waves were commonly aroused during centrifugation.

Hyperglycemia occurred after severe acceleratory shock, tissue glycogen levels were usually reduced by prolonged exposures. Other blood-chemical changes were noted. Autopsy findings even after severe tests (prostration, death) were not striking. [This work was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Univ. of Virginia.]

The rate of oxygen consumption in localized regions of the nervous system in presynaptic endings and in cell bodies. D. W. BRONK, M. G. LARRABEE AND P. W. DAVIES (by invitation). *Johnson Foundation, Univ. of Pennsylvania*. The rates of oxygen consumption by the cerebral cortex and by sympathetic ganglia of cats have been measured by the oxygen electrode devised by Davies and Brink. In the first instance this was done by forcing the electrode firmly against the cortex. The pressure of the electrode stops blood flow to the area in which oxygen tension is being measured. Accordingly, the rate of fall of electrode current is an index of the rate of oxygen consumption in the localized area of the cortex. An electrode thrust into a sympathetic ganglion similarly indicates the rate of oxygen consumption when the circulation of the ganglion is arrested.

The oxygen tension falls linearly until it reaches 2 or 3 mm Hg. There the rate of consumption changes and becomes very small. The linear decrease in tension shows that the rate of oxygen consumption is independent of tension above several mm Hg.

The time required for the cortical cells to reduce the oxygen tension in their environment to this low value is from 1 to 10 secs. In the ganglion the consumption is much less rapid, even with maximal activation the tension does not approach zero in less than 90 secs.

The relative demands for increased oxygen during activity of the several portions of the neural pathway (fibers, presynaptic endings, cell bodies) have been studied by comparing the rates of oxygen consumption during rest, during preganglionic stimulation, during antidromic stimulation, and

with preganglionic stimulation during curare block.

The circulatory effects of local variations in intrathoracic pressure. JOHN M. BROOKHART (by invitation) AND T. E. BOYD, *Loyola Univ. School of Medicine, Chicago*. Cardiometer recordings (method of Patras, Brookhart and Boyd, 1944) indicate a diminution in cardiac output and stroke volume accompanying the collapse of arterial pressure produced by pressure breathing in anesthetized dogs. Records of venous pressure vs. intrathoracic pressure (minimal free pneumothorax), obtained during pressure breathing without a cardiometer show no diminution or a slight elevation. Venous pressure registered against pressure in a small balloon between the wall of the left lung and the pericardium falls during pressure breathing in a manner consistent with the changes of cardiac volume and arterial pressure.

Differential pressure recorded between a minimal free pneumothorax and a small flaccid balloon between the left lung and pericardium indicates that extracardiac pressure is slightly higher than "intrathoracic" pressure, the difference being accentuated during pressure breathing. Introduction of air (1 to 5 cc) into a small flaccid balloon between the chest wall and the inflated lung raises pressure in the balloon above that in a free pneumothorax.

It is concluded that variations of pressure between the lung and adjacent structures may occur locally wherever the lung is prevented from assuming the shape it would assume if inflated to an equal volume in air. Such distortion of the lung reduces the component of tension tending to pull the lung away from the adjacent surface, and thus increases local pressure between the surfaces. It is further concluded that under some conditions the heart produces such a distortion, thus rendering invalid measurements of effective filling pressure made in the conventional manner.

Mechanical factors in the production of spinal cord injury by gunshot wounds to the vertebrae. J. M. BROOKHART (introduced by W. F. WINDLE). *Inst. of Neurology, Northwestern Univ. Medical School, Chicago*. (Read by title.) It is known that gunshot wounds of the vertebrae may produce cord lesions without damaging the neural canal. Thirty-five etherized cats were wounded in the region of the spinous processes of thoracic (25) and lumbar (10) vertebrae by $\frac{1}{8}$ inch steel balls having impact velocities between 3000 and 3500 feet per second. Severity of neurological signs was correlated with location of wound. The neural arch was undamaged.

Shots passing the cephalic or caudal edge of thoracic spinous processes produced signs of severe cord damage. Shots striking the middle of thoracic spines produced minimal or no cord signs. The

results suggest that rotation about a longitudinal axis is innocuous, that cavity formation in paravertebral muscles producing rotation of vertebrae about a transverse axis causes damaging shear strain in the spinal cord. Bone damage does not always accompany cord lesions in the thoracic region.

In the cat, mobility of lumbar vertebrae is limited. Severity of cord damage varies with proximity of the shot to the thin roof of the neural canal. It appears that either the shock wave or momentary depression of the roof of the neural canal by the expanding cavity produces compression of the spinal cord. Bone damage always accompanied lumbar cord damage.

It is suggested that vulnerability of the cord to damage from hits or near-hits on vertebrae is determined in part by mobility of vertebrae in various portions of the vertebral column [Work done under contract, sponsored by CMR, between OSRD and Northwestern Univ.]

Activity and the development of obesity
CHANDLER McC BROOKS *Dept of Physiology, Johns Hopkins Univ, School of Medicine, Baltimore 5, Maryland* (Read by title) The activity of rats before and after production of obesity-inducing hypothalamic lesions was determined by measuring spontaneous running in a freely revolving wheel or by recording motions imparted to a cage mounted on sensitive tambours. Immediately after operation there was characteristically a 24 to 48 hour period of intense activity followed by a period of abnormal quiescence of slightly longer duration. Running remained subnormal in seven potentially obese rats studied and finally ceased altogether as they became obese and unable to run. Tambour recorded activity of eight other animals increased progressively, after this period of quiescence, as the rats became obese, and finally rose above normal, largely because small motions which the tambours could not record when made by a rat

normal weight had a profound effect on the tambour system when made after development of obesity. Both methods showed a reduction in activity during the early part of the dynamic phase of obesity. Although running ceased the energy requirement for activity obviously increased as the animals became obese. This probably contributed to establishment of the static phase. Underactivity was, at most, merely a contributory cause of obesity because similar degrees of underactivity were produced without obesity resulting. The described reduction in activity can contribute to adiposity since appetite and food intake are not correspondingly modified. It likewise may enable a potentially obese animal to accumulate some adipose tissue even when the food intake is limited to that of a normal control.

A study of oxygen consumption in obesity

CHANDLER McC BROOKS AND DAVID N MARINE (by invitation) *Dept of Physiology, Johns Hopkins Univ, School of Medicine, Baltimore, 5, Maryland* The oxygen consumption of 18 female rats was determined once or twice weekly for several months before obesity-producing hypothalamic lesions were made in 14 of them. After operation the rate of O_2 use fell below that of the controls. Seven of these animals were fed ad libitum. As they became obese the O_2 use per gram of body weight fell even farther below normal but the total oxygen consumption gradually rose and eventually exceeded the normal. Four other rats were prevented from quickly outgaining their controls by pairfeeding. In these the total O_2 intake as well as the O_2 per gram remained significantly below normal, even though the animals did become slightly obese, until unlimited food was given. This lowered metabolism, which apparently is present in some cases of experimentally produced obesity, however, cannot be the primary cause of obesity because 1) in various animals reductions in O_2 requirement are not proportional to the obesity developed, 2) comparable reductions in metabolism can be produced without causing obesity, 3) O_2 consumption can be maintained at a normal level by means of thyroxine without preventing development of obesity (3 cases). It is thought that a reduction in metabolism requirement may help explain why some potentially obese animals can attain a degree of obesity when limited to the food intake of a normal rat.

Mechanism of fertilization of eggs
MATILDA MOLDENHAUER BROOKS *Univ of California, Berkeley, Cal* In a previous preliminary report the writer demonstrated a direct relation between the rate of O_2 consumption of unfertilized eggs, fertilized eggs and sperm of *Arbacia punctulata* on the one hand, and the redox potential of concentrated suspensions of these substances. The redox potential of unfertilized *Arbacia* eggs is low compared with that of sperm. The O_2 consumption of unfertilized eggs is also low (Warburg, etc.) but the rate rises 4 to 6-fold upon fertilization. It was therefore suggested by the writer that the high redox potential of the sperm was the important factor in initiating development.

In the present paper two other forms have been used, *Asterias forbesii* and *Chaetopterus*. In the first case, the rate of O_2 consumption of unfertilized eggs is high and there is no appreciable change on fertilization (Loeb, etc.) One would therefore expect that the redox potential of these unfertilized eggs to be high and about the same as that of sperm. This was found to be true. In the case of *Chaetopterus*, Whitaker found that the rate of O_2 consumption of unfertilized eggs was high and that there was a decrease in rate on fertilization. It was found by the writer that these unfertilized

eggs have a high redox potential which is higher than that of sperm. In conclusion, therefore, it appears that a definite redox potential is necessary to initiate fertilization, that this differs with the species, being either raised or lowered according to the state of the unfertilized egg.

The activation of myosin-ATPase by pressure in the presence of calcium. DUGALD BROWN AND H. CLAIRE LAWLER (by invitation) *Dept. of Physiology, the Graduate School and the Dental College, New York Univ.* The activity of the myosin-ATPase calcium system was determined at pressures from 200 to 800 atmospheres. The reaction mixture contained myosin 5×10^{-3} per cent, glycine buffer pH 8.4, ionic strength 0.139×10^{-2} N calcium, ATP 350 mg per cent. A reaction period of 40 minutes at 30° with a compression period of 30 minutes was employed.

Pressure enhances the activity only in the presence of calcium. The effect is reversible immediately upon decompression. The maximum pressure effect is a fourfold activation at 800 to 900 atmospheres. The extent of the pressure activation is independent of calcium concentration from 0.59×10^{-2} N to 3.9×10^{-2} N, the optimum concentration.

The decrease in volume per mol of the reaction products as compared to the reactants i.e. ΔV is 300 cc. This value is similar to the ΔV for the tension developed in the pressure contracture of muscle. In contrast the solution of myosin gels by pressure has a ΔV of 120 cc. [Assisted by a grant from the Dazian foundation and the Cinchona Products Inst.]

Changes in specific gravity and body fat of young men under conditions of experimental semi-starvation. JOSEF BROZEK (introduced by Ancel Keys) *Laby. of Physiological Hygiene, Univ. of Minnesota, Minneapolis, Minnesota*. Thirty-four men—average age 25.4 years, min 20, max 33—were maintained for 24 weeks on a semi-starvation diet. Specific gravity was determined by weighing in air and in water, at maximal expiration, according to the Archimedeian principle. An average of 1,450 cc was used as an estimated value for residual air.

The average control value of sp. gr. was 1.071, (range 1.046 to 1.086). By mid-starvation the average rose to 1.084 (range 1.052 to 1.112) and at the end of starvation to 1.089 (range 1.058 to 1.118).

The relative amount of body fat was estimated by the formula of Rathbun and Pace: % fat = $100[(5.548/\text{sp. gr.}) - 5.044]$. In standardization the calculated body fat, in kg., averaged 9.62 (range 4.2 to 20.6), in mid-starvation 4.44 (range 0 to 15.2), at end of starvation 3.08 (range 0 to 11.9). These represent changes of 55.3% and 68.0% of the control fat value as compared with average

losses of 16.6% and 22.3% of the total body weight for the same periods.

The technique was satisfactorily reliable. In 133 pairs of measurements repeated in 3 to 7 days calculated body fat values, as percentage of body weight, agreed within $\pm 1.5\%$ in 90 per cent of the cases. However, two factors tend to produce an underestimate of fat loss. Independent measurements demonstrated increasing hydration during starvation thereby reducing specific gravity. Residual air space probably increased owing to a reduction of intra-thoracic tissues and decreased power of the expiratory muscles. [This work was supported in part under a contract with the Office of Scientific Research and Development Support from other sources will be acknowledged in final publication.]

Blood flow in the bronchial artery of the anesthetized dog. H. D. BRUNER (by invitation) AND C. F. SCHMIDT *Dept. of Pharmacology, Univ. of Pennsylvania, Philadelphia*. Blood flow was measured in the right bronchial artery of heparinized dogs under chloralose or pentobarbital by passing blood from a major artery through a bubble flowmeter into the bronchial artery. Artificial respiration could be discontinued afterward by closure of the wound.

Under these circumstances, "normal" bronchial blood flow was found to be of the order of 3 to 8 cc per minute in dogs weighing between 11 and 20 kg, i.e. less than one per cent of the cardiac output, qualification is necessary because of extensive collateral connections and extra-pulmonary branchings of the artery. The flow can be labile and temporary cyclic increases were encountered occasionally, the origin of which is unknown. The vagus carries dilator fibers while branches of the stellate ganglion carry constrictor fibers. Also investigated qualitatively were the effect of variations in lung inflation by the pump, the effects of various hemodynamic drugs, and the effects of ventilation by gases of varying composition.

The preparations deteriorated with time in that the blood flow decreased, this is due in part at least to reduction of circulating blood volume from blood loss at the incisions. [This work was done under contract with the Office of Scientific Research and Development.]

Trial of the thermistor as a means of estimating blood flow. H. D. BRUNER AND W. E. STEPHENS (introduced by C. F. Schmidt) *Depts. of Pharmacology and Physics, Univ. of Pennsylvania, Philadelphia*. The thermistor is a glass enclosed electrical unit whose resistance changes exponentially with the reciprocal of its temperature which is subject to ambient temperature and joule heat from electric current. Its obvious possibilities as a rheometer in vivo were tested in pump-

operated schema using distilled water, V-597 thermistor units¹ (0.38 mm dia.) were mounted centrally in a stream which simulated *in vivo* linear pulsatile velocities and flow. The requirement that the shell temperature never exceed 42°C limited power input and necessitated operation well below optimal sensitivity.

A single thermistor as one arm of a balanced wheatstone bridge circuit commonly showed the same resistance change per 0.33°C (at 38°) as for mean linear velocity changes of 18 to 2.5 cm/sec.

To compensate for temperature, suitably paired thermistors formed adjacent arms of the bridge using 0.2 ma D.C. for balancing and a supplementary 20,000 cycle current for heating one thermistor. The results with this circuit were: 1) Careful matching of operating resistances may provide reasonable temperature compensation, e.g., the resistance change per degree C (at 38°) was 0.2 that of a mean linear velocity change from 21 to 4 cm/sec. 2) The change of resistance is a non-linear function of flow as the response is a complex averaging of the pulsatile flow, changes of pulse characteristics, total flow being constant, altered the calibration. 3) Occasional systematic shifts in resistance suggest instability in the unit as mounted. 4) Adjustment of the A.C. heating current was extremely critical.

Even if instrumental difficulties could be overcome, the delicacy and the non-linear response make *in vivo* use doubtful. [This work was done under contract with the Office of Scientific Research and Development.]

The influence of diet on uropepsin elimination
G. R. BUCHER (introduced by R. Hafkesbring)
Dept. of Physiology, Woman's Medical College of Pennsylvania, Philadelphia. Control values were established from a study of the diet records and analysis of 24-hour urines of 15 female college students for three consecutive days. Experimental values were similarly obtained for the second and third days of a three-day period during which the girls consumed their usual (control) caloric intake of special food types. Group I, (5 girls) selected only protein (meat, eggs, fish, cheese), group II, (4 girls) took only milk, group III, (4 girls) took only orange juice, group IV, (2 girls) selected an all carbohydrate diet. The records were evaluated for protein and caloric intake, the urines were analyzed for pH, total nitrogen and pepsin.

Group I, almost doubled their uropepsin output in urines of slightly increased acidity and volume. Group II, showed no changes in uropepsin output, the urine volumes doubled and all were slightly more alkaline than controls. Group III, reduced

their uropepsin outputs by half in urine volumes that were doubled and alkaline (Mean pH, 7.56). Group IV, reduced their uropepsin output by $\frac{1}{2}$, volumes and pH were unchanged. The protein in the diet and the pH of the urine appear to be factors which influence uropepsin output. The mechanisms by which these operate are being studied. [Aided by a grant from the Committee on Therapeutic Research, Council on Pharmacy and Chemistry, American Medical Association.]

Shift from negative to positive brain potential in the human during general anesthesia
W. E. BURGE, *Dept. of Physiology, Univ. of Illinois, Urbana, Illinois* (Read by title). When an electrode was placed on the forehead and another on the forearm with a galvanometer in the circuit, the forehead of unanesthetized humans was found to be positive to the forearm.

General anesthesia during surgical operations on thirty-two humans of various ages and conditions with the use of the different more commonly used anesthetics caused a decrease in the positive potential of the forehead, and in deep surgical anesthesia brought about a reversal in polarity in twenty-nine of the thirty-two subjects, that is, caused the scalp of the forehead to become negative to the forearm. Upon recovery from anesthesia, polarity again reversed, and the scalp became positive.

We have found in etherized dogs with trephined skulls (*Anesthesiology*, Vol. I, No. 1, 1945) that the positive potential of the scalp of dogs fluctuated with the negative potential of the underlying brain cortex in a 1 to 8 ratio, so scalp potential may be used as an index to brain potential.

Hence, if the relationship between scalp and brain potential of humans and dogs is comparable, the fall in the positive potential of the scalp of humans during surgical anesthesia described above indicated a fall in the negative potential of the underlying brain cortex, and the reversal in polarity in deep surgical anesthesia indicated that the brain cortex had become positive in deep narcosis, thus confirming for humans observations made by us in 1936 on dogs (*Anesthesia and Analgesia*, Vol. XV, No. 2, 1936).

The oral administration of protein hydrolysates
D. BAILEY CALVIN AND EDGAR J. POTH (by invitation). *Depts. of Biological Chemistry and Surgery, Univ. of Texas, Medical Branch, Galveston*. Partial acid hydrolysis of casein yields products which are tasteless if the hydrolysate does not contain amino acids. Various of these products (Essenamine,¹ M and MC modifications of Essenamine) have been studied to determine absorption, excretion, maintenance of plasma protein levels, and nitrogen balance.

¹ Obtained from the Western Electric Company through the courtesy of Mr. J. E. Tweeddale.

¹ Furnished by Frederick Stearne.

The physical characteristics of these substances are such that large quantities can be administered by ingestion, or by stomach tube if necessary, to give high nitrogen intake in a practically residue free diet

The plasma protein level, and a positive nitrogen balance has been maintained over a period of four months when no other source of nitrogen containing food was available

Sodium succinates as an analeptic in man
C J CAMPBELL (by invitation), J P MAES, AND R H BARRETT (by invitation) *From the Dept of Physiological Sciences, Dartmouth Medical School* Fifty surgical patients in deep pentothal sodium anesthesia received intravenous injections of a sterile 30% aqueous solution of disodium succinate hexahydrate (Brewer Company, Worcester, Massachusetts) in amounts varying from 2 to 200 cc. No toxic symptoms occurred. The sequence of events was usually dramatic. Typically within 15 to 20 seconds the patients coughed, Within 30 to 120 seconds a deep flush appeared in the blush area. The respiratory rate increased transiently and the blood pressure returned to preanesthetic levels. With adequate amounts, the individual would be awake and oriented in 10 to 15 minutes. Ambulatory patients were able to walk unassisted within 20 minutes. Isosmotic solutions of NaCl failed to produce similar results.

In 8 cases of attempted suicide by other barbiturates and in 2 cases of morphine poisoning the results were similar.

In normal unanesthetized human volunteers 5 cc of 10% solution injected intravenously produced no toxic effects. A blush appeared as described above, accompanied by a feeling of warmth. Flushing was sometimes succeeded by pallor within 1 minute. Oxygen consumption, respiratory rate and depth, blood pressure and pulse rate were but transiently and slightly affected. The oral temperature did not change. The outstanding symptoms (20-30 seconds after injection) was a transient feeling of suffocation. This was followed by approximately 30 seconds of irregular respiration.

One cc of 30% succinate was injected intravenously into decerebrate cats. Within 20 seconds there occurred for 2 or 3 respiratory cycles an exaggeration of the normal respiratory movements of the glottis.

Studies of stilbestrol monomethyl ether
A CANTAROW, A E RAKOFF (by invitation), AND K E PASCHKIS *Jefferson Medical College, Philadelphia, Pa* (Read by title) Large amounts of estrogen were found in the bile of menopausal women receiving therapeutic doses of stilbestrol monomethyl ether orally, and in the bile of dogs after intravenous and intramuscular injection. Biliary excretion of estrogen continued for at least 11 days after intramuscular injection. Evidence

was obtained that at least a portion of the biliary estrogen after intravenous injection is in the form of stilbestrol monomethyl ether.

Rats injected intramuscularly with 100 gamma continued in estrus for 12-20 days. With this dosage, no estrogenic activity could be demonstrated in the injected tissues or the viscera after three days. When 1 mg was injected, extraction of the injected tissues after three days yielded quantities of estrogen equivalent to 10-20% of that injected when the volume of oil employed was 0.1 cc and 40% when the volume of oil was 1.0 cc. After six days, these values were less than 6% and about 30% respectively.

These data suggest that the prolonged estrus after relatively large intramuscular injections of stilbestrol monomethyl ether probably are not due entirely to a local deposit effect and that the latter depends to some extent upon the volume of oil in which the estrogen is injected. Administration of this estrogen is followed by biliary excretion of large amounts of estrogenically active material, as has been found previously with stilbestrol, alpha-estradiol, ethinyl estradiol and estrone.

Physiologic effects of bilateral cerebellar removals in the primate
R M E CARREA (introduced by Fred A Mettler) *Dept of Neurology, College of Physicians and Surgeons, Columbia Univ, N Y C* Disturbance of equilibrium follows removal of flocculus, or nodulus, uvula and lingula (less marked and different in former). Symptoms are more marked if paraflocculus is also removed (parafloccular removal alone is unproductive) and more enduring if occipital lobes are ablated. Unsteadiness, common in all cerebellar removals, is most conspicuous in these lesions. Ablation of remaining vermis produces transient trunk ataxia, without abduction, and intermittent fine, rapid, static head tremor. Similar results follow ablation of roof nuclei, but tremor is more conspicuous.

Removal of lobulus paramedianus, ansiformis and pyramid produce transient weakness, decreased resistance to passive movement and reduced motor performance in legs. Ablation of culmen and lobulus simplex produce dysmetria and intention tremor in homolateral upper limbs (which recover in forty days) and transient reduction in motor performance of homolateral leg. Summation of the two last mentioned removals produces coarser dysmetria, more marked intentional tremor (persisting during relaxation) and more pronounced ataxia and reduction of motor performance. Removal of dentates produce intense ataxia and coarse dysmetria which at first present only during activity, finally becomes established at rest. Extensive removals of cortex and nuclei produce a compound of the above mentioned disturbances but there is neither static shaking nor tremor. Complete recovery has not occurred in eighty days.

Postoperative extensor increase in resistance to passive movements was present immediately after removal of dentates and after complete decortication and for two days after extensive decortication with removal of the nuclei

Recovery is impaired by enduring reduction of motor performance

Number of spermatozoa required for the fertilization of superovulated eggs in the rabbit M C CHANG (introduced by G Pincus) *Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts* The relation of the number of eggs to the number of spermatozoa required for fertilization was examined In mature animals (1) Ovulation induced by sterile copulation or gonadotrophin produced an average of 9 eggs and required a minimal sperm number of 475,000 inseminated artificially to fertilize all eggs (2) Reduction to 92,000 resulted in 57% fertilization (3) Superovulation induced by gonadotrophin resulted in 24-73 eggs 73% were fertilized by the same sperm concentrate as used in (2) (4) In superovulation, varying the number of sperm from 80,000 to 40,000, a marked decrease in the percentage of fertilized eggs was obtained (7-14%) In "normal" ovulation, no fertilization was obtained with this amount of sperm (5) Thus the number of eggs to be ovulated appears to be of no significance in determining the minimal sperm concentration in mature animals

In immature animals 13 does were ovulated using gonadotrophin yielding 2 to 10 eggs When sperm concentrations varying from 475,000 to 65,000 were inseminated only 1 of 51 eggs (2%) were fertilized 9 does superovulated by repeated injections yielded 15 to 75 eggs per doe Using a sperm concentration of 238,000 to 65,000, 11 eggs from 5 of the 9 does were fertilized altho the percentage was only 3.4 Here either the high number of eggs or the maturing of female organs due to longer injection time may explain the finding

Representation of muscles in the motor cortex of the macaque H T CHANG (by invitation), T C RUCH and A A WARD, JR (by invitation) *Laby of Physiology, Yale Univ School of Medicine, New Haven* The responses to cortical stimulation of the muscles acting over the ankle joint have been recorded kymographically with isometric levers Eight muscles were recorded simultaneously from muscles "isolated" by appropriate dissection of tendons and nerves of the legs, all muscles acting over the ankle have been examined in different experiments The leg area was systematically mapped mm by mm, using unipolar electrodes and a Goodwin stimulator Nine monkeys under light Dial anesthesia were employed Considerable variation in the maps from animal to animal was found, but a much greater consistency of response pertains for a given monkey on the same or successive days Anatomical flexor muscles, with the

exception of tibialis posterior were rarely responsive Tibialis anterior, Abductor hallucis longus, Extensor digitorum longus, and Extensor hallucis longus and Tibialis posterior were most active Restricted regions or bands are found from which single muscles or a fraction of the muscle group are most readily activated This is manifested by threshold, tension production and latency, and speaks for a concentration of representation of single muscles Areas relatively silent for all muscles under observation were found In two experiments benzedrine greatly increased the responses to cortical stimulation

The dark adaptation of the color anomalous. A CHAPANIS (introduced by E A Pinson) *Laby of Physiological Psychology, Yale Univ, New Haven, Conn, and Aero Medical Laby, Air Technical Service Command, Wright Field, Dayton, Ohio* Dark adaptation measurements using red and violet test lights were made with a Hecht-Shlaer Adaptometer under three conditions (1) 3° light viewed 7° temporally, (2) ½° light viewed centrally, and (3) ½° light viewed 7° temporally The subjects were six deuteranopic or deuteranomalous, eight protanopic or protanomalous, and eight color normal individuals

Dark adaptation curves for the deuteranopic and deuteranomalous subjects are indistinguishable from those for color normal subjects

Violet dark adaptation curves for the protanopic and protanomalous subjects are normal For the same subjects, red dark adaptation curves measured 7° peripherally with the 3° light reach an initial plateau about 1½ log units above the normal thresholds to red light during the first 12 minutes, show a second decrease from 12 to 22 minutes, and form a second plateau with normal threshold values from 22 to 40 minutes Foveal thresholds measured with the ½° red light reach a level about 1½ log units above normal during the first eight or nine minutes and do not change thereafter Peripheral measurements with the ½° red light resemble those made with the 3° red light except that the terminal thresholds from 22 to 40 minutes remain about ½ log unit above the normal values

Although these data are not in agreement with certain recent hypotheses regarding the rod function of the color blind, they are consistent with and can be derived from other known data regarding the sensitivity of the rods and cones

The effect of sex hormones on the dominance-subordination relationships of the castrate female chimpanzee GEORGE CLARK and HERBERT G BIRCH (by invitation) *Yerkes Labys of Primate Biology, Orange Park, Florida* The validity of the concept that rise in estrogen level decreases aggressiveness and evokes submissive behavior is made questionable by the fact that in the female chimpanzee increase in dominance accompanies

autogenous cyclical rise in estrogen level. This information comes from observations on intact animals in whom hormone level was uncontrolled. In the present study three ovariectomized, and hysterectomized adult females were studied to determine the effects on social-dominance behavior of constant dosages of alpha-estradiol (2 mg/day) and methyl-testosterone (50 mg/day).

Both androgen and estrogen reliably improved the dominance score of the treated animal in a food competition situation. The increased dominance under androgen persisted for several weeks after cessation of treatment. Estrogen therapy increased dominance in proportion as it produced swelling and engorgement of the ano genital area, and dominance so induced disappeared with detumescence. Since estrogens induce submissive behavior in the male-castrate chimpanzee in whom no genital swelling occurs, it seems likely that it is the irritative effect of swelling which tends to increase aggressiveness in the estrogen-dosed female chimpanzee.

An examination of the literature on mating behavior, and social-dominance behavior of female mammals, indicates that estrogen-dominance is not unique in the female chimpanzee. It seems that the general theory of submissiveness as a female characteristic has arisen out of a confusion of the female role in the mating *per se* with submissiveness. Little valid evidence exists to support such a contention.

Effect of ingestion of food and fluid on tolerance of human subjects to positive acceleration. WILLIAM G. CLARK and HELEN JORGENSEN (by invitation) *Dept. of Aviation Medicine, Univ. of Southern California, Los Angeles*. The effects on gram tolerance of the ingestion of 1.5-2.0 liters of water or milk, or a heavy meal were studied in eight centrifuge-trained subjects during the course of 200 centrifuge runs. The centrifuge attained maximum acceleration at the rate of 3 grams per second and maintained it for 15 seconds. Tolerance to gram was determined from recorded responses to visual and auditory signals and to changes in ear opacity (blood content of the ear). In addition, intrarectal pressure changes were recorded.

A small increase in gram tolerance was induced by a full stomach which averaged 0.3-0.4 gram (range from 0.0 to 1.1 gram). In relaxed subjects with an empty stomach, the average increase per gram in intrarectal pressure was 18.5 mm Hg. The increase due to fluid ingestion is slightly greater, being 7-9 mm Hg at 3 and 4 grams, respectively. The intrarectal pressure increase induced by voluntary muscular and respiratory straining is of the order of 40 mm for 1 gram protection. When divided into 7-9 mm, this gives 0.2 gram protection at this level of gram, which is good agreement.

From the work of others, blood pressure increases

due to fluid or food ingestion are too slight to explain the effect. Fluid and food ingestion has been shown by others to increase cardiac output without evoking vasomotor mechanisms or causing displacement of blood from the somatic tissues to the visceral organs. Increase in intra-abdominal pressure caused by the ingestion seems the logical explanation of the effect, just as gram tolerance can be enhanced 0.5-0.8 gram by increasing intra-abdominal pressure by pressurized abdominal belts and bladders in anti-blackout suits. [The work described in this abstract was done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development, and the Univ. of Southern California.]

Effect of hyperglycemia and insulin hypoglycemia on man's tolerance to positive acceleration. WILLIAM G. CLARK, I. D. R. GARDINER (by invitation), A. K. MCINTYRE (by invitation), and HELEN JORGENSEN (by invitation) *Dept. of Aviation Medicine, Univ. of Southern California, Los Angeles*. (Read by title). Hyperglycemia induced by the ingestion of two grams of sugar per kilogram body weight, and insulin hypoglycemia at a level of 50-55 mg % blood sugar concentration, had no significant effect on the gram tolerance of three trained centrifuge subjects, studied during the course of 43 centrifuge runs. The centrifuge attained maximum acceleration at the rate of 3 grams per second and maintained it for 15 seconds. The sugar or insulin was administered after a 12 hour fast. The centrifuge assays of gram tolerance were performed during the hypoglycemic state and were repeated after return to normal, and during the normal state after a 12 hour fast, following by the hyperglycemic state. The average units of plain insulin injected subcutaneously per kilogram per hour averaged 0.17. Tolerance to G was determined during a series of centrifuge runs at levels of gram which kept vision clear, up through those which caused blackout, by changes in recorded responses to visual and auditory signals and by changes in ear opacity (blood content of the ear). [The work described in this abstract was done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research, and Development and the Univ. of Southern California.]

The effect of positive acceleration on fluid loss from blood to tissue spaces in human subjects on the centrifuge. WILLIAM G. CLARK, I. D. R. GARDINER (by invitation), A. K. MCINTYRE (by invitation), and HELEN JORGENSEN (by invitation) *Department of Aviation Medicine, Univ. of Southern California, Los Angeles*. (Read by title). As estimated by hematocrits and plasma protein determinations, fluid loss from blood to tissue spaces occurred in six seated human subjects on the centrifuge. At near blackout levels of G (3.5 to 5.0 G) maintained for 3-5 minutes, a significant

loss of fluid (3.6-4.5 cc /100 cc blood, or 216-270 cc total) was found. The loss in four subjects exposed to 4 G for 5 minutes was reduced by anti-G suits to an average of 75% (range 28-96%) of their loss when unprotected. In two cases subjected to 3.5 G for 5 minutes, the loss was less than that of the four subjects exposed to 4.0 G for 5 minutes. In one subject submitted to 5 G for 3 minutes, the loss was less than that he obtained at 4 G for 5 minutes, although after-effects were noticed in vision. A smaller loss (132 cc total) occurred in one of the subjects who had 30 runs of 4.7 G for 10 seconds with a 2 minute interval between runs, than occurred in the same subject after a 5 minute uninterrupted run at 4.0 G (288 cc).

At 4.0 G, the fluid losses observed were much less than those reported elsewhere for centrifuged dogs, but recovery occurred more rapidly. The losses also were less than those reported elsewhere for postural changes of humans from the recumbent to the upright positions. It is unlikely that fluid losses due to G contribute to any fatiguing effects or detrimental residual effects possibly resulting from positive acceleration experienced by test pilots or fighter pilots in combat. [The work described in this abstract was done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development, and the Univ. of Southern California.]

The effect of environmental temperature upon man's G tolerance. C. F. CODE, E. J. BALDES, E. H. WOOD, and E. H. LAMBERT, *Acceleration Lab., Mayo Aero Medical Unit, Rochester, Minnesota*. The g tolerance (capacity to withstand increased positive accelerative forces) of fifteen normal men has been studied in a cool environment (average 63°F, 72 per cent relative humidity) and contrasted with that obtained in the same subjects in a warm humid environment (average 89°F, 77 per cent relative humidity).

The g tolerance was determined on the human centrifuge (accelerator) by means of an assay procedure based upon the recognition and recording of the subjective visual symptoms and the objective measurement of changes in ear opacity (blood content of ear), ear pulse and heart rate during exposures to acceleration (g).

As determined by these criteria the g tolerance of the group was uniformly lower in the warm than in the cool environment. The visual symptoms, ear opacity, ear pulse and heart rate changes of the group showed average reductions in tolerance of 0.9, 0.7, 0.8 and 0.7 g, respectively, indicating that in the warmer environment the overall g tolerance of the subjects was lower on the average by 0.8 g. [Work done under contracts with (1) United States Army Air Forces, Wright Field, Dayton, Ohio, and (2) the Office of Scientific Research and Development, National Research Council, Washington, D. C.]

Hydrostatic anti-blackout protection, the protection afforded man against the effects of positive acceleration by immersion in water (motion picture). C. F. CODE, E. H. WOOD, E. J. BALDES, *Acceleration Lab., Mayo Aero Medical Unit, Rochester, Minnesota*. The motion picture shows the methods used in this study and illustrates the average protections afforded man against the effects of positive acceleration by immersion in water.

The study was carried out on the human centrifuge. A specially constructed bath tub was placed in the gondola or cockpit of the centrifuge. The subjects sat in this tub in the same position as that assumed by a pilot in a fighter airplane. Each test included the determination of the subject's g tolerance while sitting in the tub—first, without water, then with water added to various body levels, and finally again without water as a re-check of the control determinations. On the average, immersion in water to the xyphoid gave 0.9 g protection and immersion in water to the level of the third rib gave 1.7 g protection. [Work done under contracts with (1) United States Army Air Forces, Wright Field, Dayton, Ohio, and (2) the Office of Scientific Research and Development, National Research Council, Washington, D. C.]

Some relationships in the response of rectus abdominus muscle to acetylcholine and potassium. SAUL L. COHEN (introduced by Robert Gesell), *Univ. of Michigan*. Assays for acetylcholine in brain extracts by use of the frogs' rectus abdominus showed disproportionate variations with dilution. The possibility that the interfering substance(s), which continued to give a reaction after alkali destruction of the acetylcholine, might be potassium was investigated.

The test muscle showed responses to the presence of excess potassium (2-6 times the amount in normal Ringer's solution) similar to those shown for acetylcholine. The response to solutions containing both acetylcholine and excess potassium was essentially one of summation. The dose-response curve for potassium, however, is much steeper than for acetylcholine, this might be expected for the substance(s) responsible for the assay difficulties of brain extracts. That potassium elicits a muscle response by some method other than through effecting a release of acetylcholine is also indicated by (1) the failure of eserization to enhance the response to potassium and by (2) the differences of CO₂ and NaHCO₃ influences on the muscle response to potassium and acetylcholine. The sensitivity of the muscle to test solutions was enhanced by repeated exposure to either nerve-tissue extracts (cf. also Feldberg, 1943) or to the "excess potassium" solutions.

The possibility that potassium in nerve-tissue extracts is responsible for the limitations in the frog muscle tests for acetylcholine is thus supported.

Plasma renin substrate levels during adrenal insufficiency W D COLLINGS, ERIC OGDEN and A N TAYLOR (by invitation) *Dept of Physiology, Univ of Texas Medical School, Galveston, Texas* Assays of plasma renin substrate were done before and during 5 episodes of adrenal insufficiency in 3 adrenalectomized dogs and on 2 dogs during recovery from adrenal insufficiency

Renin substrate content was assayed by injecting into pithed or anesthetized cats 0.5 to 2.0 cc of plasma mixed with 0.3 unit of hog renin per cc of plasma. Before testing, the mixture was incubated for 10 minutes at room temperature. The sensitivity of each assay animal was checked against normal dog plasma and a "standard" angiotonin preparation

Clinical signs of adrenal insufficiency were produced by stopping supportive injections of desoxycorticosterone acetate. The fall in blood pressure which is a late result of insufficiency apparently begins before any detectable change in the plasma renin substrate content. Terminally, substrate fell to one half or less of the original level. Under supportive therapy, recovery from insufficiency was generally complete in a week or less but the substrate level was not restored until the 5th week.

To imitate the hemoconcentration and blood pressure decrease characteristic of adrenal insufficiency, one dog received 70 cc per kg of 5.5% glucose intraperitoneally. This produced a 15% increase in hemoglobin and packed red cell volume and a drop in blood pressure from 125 to 74 mm Hg. No change in plasma renin substrate was detected although blood samples were taken at 1.5 to 2 hour intervals. [Aided by the John and Mary R. Marlic Foundation]

Crush syndrome (post-traumatic anuria) A C CONCORAN and IRVINE H PAGE *From the Research Division of the Cleveland Clinic Foundation, Cleveland, Ohio* A study of crush syndrome has shown (1) that excretion of myoglobin by aciduric normal dogs causes recoverable renal injury, the degree of which is proportional to the amount of pigment retained and which affects chiefly tubular secretory capacity (2) Injection of large doses of hematin in normal dogs causes severe renal injury (3) The injury caused by myoglobinuria may be due to conversion of retained pigment to hematin within the tubule

(4) Prolonged hypotension due to bleeding provokes a renal vasoconstriction which is not released by transfusion of blood and (5) a more intense and immediate vasoconstriction is elicited by application of limb tourniquets. By exclusion of other factors and by demonstrating vasoconstrictor substances in the blood after bleeding or tourniquet application it was concluded that this vasoconstriction is humoral in origin and probably due to substances released from injured tissue. Since in dogs (6) the degree of persisting renal injury caused by myoglobinuria alone was not severe and

since severe vasoconstrictive renal ischemia due to bleeding or tourniquet application alone or combined with myoglobin injection more commonly resulted in death from shock than survival with renal failure, we turned to the study of another species

In rats (7) severe renal injury follows crushing of one hind leg when combined with infection of myoglobin. A lesser injury results from crushing without myoglobin injection, and myoglobin injection in normal, aciduric rats causes no significant damage. We therefore conclude (8) that clinical crush syndrome is probably the combined result of vasoconstrictive renal ischemia and simultaneous liberation of myoglobin into the blood. [The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Lilly Lab for Clinical Research, Indianapolis City Hospital]

Clinical standardization of the antimalarial properties and the toxicity of plasmochin administered alone and concurrently with quinine. BRANCH CRAIG, JR., (by invitation), RALPH JONES, JR., (by invitation), THEODORE PULLMAN, (by invitation), C MERRILL WHORTON, (by invitation), LILLIAN EICHELBERGER, (by invitation), and ALF S ALVING. *The Malarial Research Unit, Dept of Medicine, The Univ of Chicago* Sinton has reported that plasmochin and quinine given concurrently possess curative antimalarial properties exhibited by neither drug alone. Following the confirmation of this observation for the Chesson strain of vivax malaria by Shannon and his co-workers, a systematic study of these compounds was undertaken at the request of the Panel on Clinical Testing of the Board for the Coordination of Antimalarial Studies. Standardized procedures for the administration of plasmochin and quinine were developed by varying the daily dose of plasmochin in 14-day therapeutic trials during either primary, or first and second relapses of (Chesson) vivax malaria. Non-immune inmate volunteers at Stateville Penitentiary have served as subjects.

A description and discussion of the standardized procedure, which has proved useful as a standard of reference for rapid clinical evaluation of several 8-amino quinoline compounds other than plasmochin, will be presented. [Work done under contract with the Office of Scientific Research and Development]

Cardiovascular and respiratory responses to emotion in psychopathic subjects and controls L A CRANDALL, JR and T S HILL (by invitation) *From the Dept of Physiology and Psychiatry, College of Medicine, Univ of Tennessee, Memphis* Respiratory movements, changes in blood pressure, and frequently skin resistance were recorded by a Keeler polygraph. Subjects were medical students

other "normal" volunteers, and mental patients. All were asked fifty questions while records were being obtained.

Most subjects responded to some of the questions by increases in blood pressure. These increases occur within one or two seconds, and may or may not be accompanied by changes in heart rate. They are too prompt to be due to release of epinephrine, and are presumably attributable to vasoconstriction.

When the records of subjects without mental disease are compared with those of patients, certain differences are obvious. The respiratory patterns of the latter tend to be irregular in rate, amplitude, and baseline, and there are frequent sighs. This phenomenon has been observed previously (Alexander, F., and L. J. Saul, *Psychosomatic Med* 2: 110, 1940, and Keeler, L., unpublished). The blood pressure responses of these patients also tend to be prolonged (over 30 seconds) as compared with "normal" subjects.

This procedure may 1) detect abnormal visceral responses characteristic of certain mental diseases, and, 2) determine the general nature of the patient's conflicts. The latter use has proved time saving and has elucidated material not obtained by previous interviews.

Activation of tissue elements by slow neutron exposure. By H. J. CURRIS and J. D. TERESI (by invitation). *From Clinton Labys, Oak Ridge, Tennessee.* When tissue is exposed to slow neutrons, a nuclear reaction takes place between the neutrons and the various atoms of the tissue. This reaction will release energy within the tissue in the form of various types of radiation, and will also produce radioactive isotopes which slowly decay and release further energy within the tissues. The present study concerns itself with the isotope production. Phosphorus, sodium, potassium and chlorine are the most important body elements in this regard. Calculations can now be made of the quantities of these isotopes formed and their biological effects. These have been checked experimentally in two ways. In the first place mice were exposed to slow neutrons from the Clinton graphite pile, and the exposures monitored by means of copper or indium foils. The animals were sacrificed at some definite time after exposure and various tissues analyzed quantitatively for P^{32} , Na^{24} , K^{41} and Cl^{38} . In all cases the predicted amount was found within experimental error. Next, rats were exposed to slow neutrons and the excreta examined for P^{32} and Na^{24} . From an analysis of the diet, the radioactive sodium excretion was as predicted assuming the excretion to be a true aliquot of all of the Na in the body. About one-third of the phosphorus activated in this way was excreted as an aliquot of the total body phosphorus, about one-third was excreted only slowly and the remainder appeared to be immobile.

On the membrane hypothesis of the antigen-antibody reaction. SYLVIA L. D'ALBERGO (by invitation) and W. A. SELLE, *Dept of Physiology, Medical School, Univ of Texas, Galveston.* The latent period prior to the specific anaphylactic reaction of the isolated ileum of guinea-pigs was found to be the same whether a low or high molecular weight antigen was used. Guinea-pigs were sensitized to both hemocyanin (molecular weight about 7 million) and to egg albumen (molecular weight about 35,000). After three weeks segments of the ileum were treated according to the Schultz-Dale technique. A latent period of about 45 seconds was observed for each of the antigens.

If diffusion into cells takes place, there should be a longer latent period prior to the contractile response for antigens having a high molecular weight. In face of the actual demonstration that the latent period is the same whether the antigen is of low or high molecular weight, it would seem reasonable to assume that the reaction takes place on the surface of the cell as Doerr has postulated.

The respiratory exchange in human subjects during prolonged exposures to moderately low simulated altitudes. SAVINO A. D'ANGELO (introduced by Harry A. Charipper). *Aero-Medical Lab, Wright Field, Dayton, Ohio and Dept of Biology, Washington Square College of Arts and Science, New York Univ, N. Y.* (Read by title). Prolonged exposures (ten hours) to simulated altitudes of 8,000 and 10,000 ft without supplementary oxygen and under conditions of restricted food intake produced changes in the respiratory metabolism of resting human subjects. The degree of change was of the same order of magnitude at both altitude levels.

The modifications in the respiratory metabolism resulting from the prolonged stays at these altitudes were collectively indicative of a respiratory alkalosis and involved 1) an increase in pulmonary minute volume and CO_2 elimination which became progressively greater, relative to ground level values, with time of exposure; 2) elevation of the R.Q.; 3) a shifting of the urinary pH toward alkalinity in subjects showing appreciable hyperventilation (blowing off of CO_2). No significant changes in the over-all oxygen consumption, oral temperature, or respiratory rate were found.

The physiological changes which occurred during the prolonged exposures to the 8,000 and 10,000 ft levels were reflected in behavior differences (somnia, irritability, inattention, lack of volition, and fatigue) which, while not quantitatively assayed, were highly suggestive of psychologic deterioration. Obvious differences existed among subjects regarding tolerance to the prolonged exposures. Altitude tolerance appeared to be best correlated with differences in the R.Q. subjects who tolerated altitude poorly displayed little or no change in respiratory quotient, whereas, in

those tolerating exposures relatively well the R Q was significantly elevated

Urine volume and phosphorus excretion in human subjects during prolonged exposures to moderately low simulated altitudes SAVINO A D'ANGELO (introduced by Harry A Charipper) *Aero-Medical Lab, Wright Field, Dayton, Ohio, and Dept of Biology, Washington Square College of Arts and Science, New York Univ* (Read by title) Urinary secretion and phosphorus excretion were studied in five subjects over 10 hour exposure periods at simulated altitudes of 8,000 and 10,000 ft under conditions of standardized food and water intake No appreciable change in total urine output from the ground level values was found at either altitude studied The most characteristic feature of urine elimination was the considerable degree of variation encountered from run to run despite the carefully controlled food and water intake

The total urinary excretion of inorganic phosphorus was significantly decreased in all subjects at altitude The reduced excretion became apparent early in the exposure period at either the 8,000 or 10,000 foot level The rate of excretion increased with increasing exposure time The reduced phosphorus output bore no relationship to the urine output, nor could it be directly correlated with changes in respiratory metabolism or in blood sugar level

These experiments provide evidence to indicate that alterations in the mineral metabolism may occur in the human organism at altitudes as low as 8,000 ft

Autonomic and electroencephalographic effects of posture CHESTER W DARROW, JULIAN PATHMAN (by invitation) and WARREN MORSE (by invitation) *Inst for Juvenile Research, Chicago* (Read by title) Inability in certain instances to demonstrate expected autonomic effects on the electroencephalogram (EEG) suggested possible compensatory effects by moderator (carotid sinus?) nerves A test of effects of posture on autonomic activity and EEG offered an approach to the problem Emotional effects of unusual or insecure postures have, however, to be taken into account

Subjects were arranged for autonomic and EEG recording on a tilting table Blood pressures were recorded from the wrists held across the chest Tilting to a 45° feet down position typically increased blood pressure, heart rate, palmar skin conductance, and voltage of EEG at alpha frequency The effect was reversed on return to horizontal Tilting 30° from horizontal toward a head down position had variable effects depending on emotional concomitants When blood pressure and heart rate decreased with little change in skin conductance (indicating relatively uncomplicated effects) alpha potential was reduced When, as was more often the case, change toward the head down position was attended by increase of blood pres-

sure, heart rate, and palmar skin conductance (emotional effects?), there was an increase of alpha compared with level Increased heart rate and skin conductance were more consistently related to increased alpha potential than were either posture or blood pressure

Carotid sinus compensation accounts for many otherwise unexplained autonomic-EEG relations

Autonomic significance of "blocking" and "facilitation" in electroencephalogram CHESTER W DARROW, JULIAN PATHMAN (by invitation), and WARREN MORSE (by invitation) *Inst for Juvenile Research, Chicago* "Blocking" of alpha rhythm by stimulation has been explained as a breaking of thalamo cortical resonance "Facilitation" of alpha may involve increased $10\pm$ /sec driving of the cortex Thus, amount of alpha activity may represent the balance between cortical felt-work fast activity (favoring vasodilatation) and subcortical $10\pm$ /sec regulation of that activity (favoring vasoconstriction)

It is shown that when both cortical and subcortical activity are minimal (drowsiness and sleep) low level autonomic activity is associated with a flat or slow EEG, and stimuli arousing the subject elicit alpha activity simultaneously with changes indicating mobilization of the autonomic system

In the already aroused but mentally inactive individual alpha activity is optimum Under these conditions stimuli increasing cortical activity "block" the alpha rhythm However, strong emotional and autonomic (subcortical?) excitation may be attended by increased alpha amplitude Also following moderate stimuli in persons with low voltage waking EEG, increased voltage at $10\pm$ /sec in motor leads is often demonstrable during the latent period of the palmar galvanic (sympathetic) response

It is postulated that fast activity and opposed $10+$ /sec resonance in the brain provide a mechanism by which cortical and subcortical (thalamic, hypothalamic) structures mutually regulate one another Effects of these frequencies on the autonomic system may contribute to correspondence between EEG frequency and cerebral vasomotor tone

Rapid bursts of oxygen consumption in stimulated muscle P W DAVIES (introduced by D W Bronk) *Johnson Foundation, Univ of Pennsylvania, Philadelphia* Evidence has been found that there is a rapid onset of oxygen consumption during a single twitch in frog striated muscle

This has been obtained with the aid of the oxygen cathode described by Davies and Bronk (R S I, 13, 524, 1942) In these experiments the cathode was an open style antimony microelectrode applied directly to the surface of the active fibers Its current readings were proportional to muscle oxygen tension

When stimulated with a single shock, the tension in the muscle fibers quickly begins to fall, reaches a minimum within $\frac{1}{2}$ sec, and rises again to its initial level within 2 seconds. The shape of the curve indicates an initially rapid consumption which very soon falls back to a near-normal level.

If the muscle is stimulated repetitively, the successive curves summate, their separate minima being observable if the rate of stimulation is not too great.

Temporary hearing-loss following exposure to loud tones. H. DAVIS, C. T. MORGAN, J. E. HAWKINS, JR., R. GALAMBOS and F. W. SMITH (by invitation) *Dept. of Physiology, Harvard Medical School, Boston*. Nineteen men were repeatedly exposed to pure tones at 110, 120 and 130 db for 1 to 64 minutes.

Temporary impairment of hearing was regularly produced. Some men were much more susceptible than others, but none showed cumulative injurious effects.

No significant elevation of auditory threshold is produced for tones of frequency lower than the exposure tone. The greatest hearing-loss occurs about half an octave above the exposure tone. With brief exposures the loss is usually confined to the two octaves above, but with the longer exposures the hearing-loss often involves all tones above the exposure frequency. One-thousand- and 2000-cycle tones are about equally effective. 4000 cycles is more, and 500 cycles is much less effective. Hearing-loss develops most rapidly during the first minutes and then progressively more slowly. Recovery is most rapid in the first hours, but for a 60-db loss may require 4 or 5 days to be complete. Recovery for 4000 cycles is slowest whatever the frequency of the exposure tone. The loss is a "nerve deafness." With a threshold elevation of 60 db there may be only 6 db loudness-loss at the 100-db loudness-level.

A hearing-loss restricted to a narrow range of frequencies may be associated with very severe distortion of pitch-perception (diplacusis). Tones of certain frequencies sound noisy and impure or may be abnormally elevated in pitch by as much as three-quarters of an octave. The major displacements in pitch are always upward. [*The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Harvard University.*]

Hyperchromic anemia produced in dogs by choline and carbamyl choline. JOHN EMERSON DAVIS *Dept. of Physiology and Pharmacology, Univ. of Arkansas, Little Rock*. (Read by title.) Hyperchromic anemia responsive to liver extract injection was produced in dogs in this laboratory by the feeding of choline chloride (1944). The attempt was made to repeat the anemia in a similar manner in 4 of the same dogs (treated with liver

4 months earlier), but no persistent anemia resulted.

However, anemia was produced in 5 new normal dogs and one splenectomized dog. Three of the dogs received 2 doses of choline daily for 3 weeks, 2 doses of choline and 2 doses of physostigmine daily for about 16 days, and then 2 doses of choline and 2 doses of carbamyl choline daily for 3 or more weeks. The use of physostigmine did not appear to augment the anemia-producing effect of choline. Two dogs were fed choline 3 times daily, and one dog was given 3 subcutaneous injections of carbamyl choline (0.01 mgm./kgm.) daily for 5 weeks. Anemia appeared in all 6 of these dogs within 2 to 5 weeks. Their erythrocyte counts were reduced by 30 to 37 per cent. Color indices were increased by an average of 0.18, in other words to 1.18, if originally at 1.00.

The dogs were sacrificed during their anemia or at variable periods after recovery, for histologic study of their tissues. These studies are now in progress.

The change in the water metabolism and in the endocrine glands of long-surviving diabetes insipidus dogs. RICHARD C. DE BODO and DAVID MARINE *Dept. of Pharmacology, New York Univ. College of Medicine and Montefiore Hospital, New York*. (Read by title.) Severe experimental diabetes insipidus—characterized by high polyuria, urine of low specific gravity, and a very limited ability to concentrate urine on dehydration—was produced in a series of dogs by severing the supra-optico-hypophysial tract and observed for a period of about four years. Approximately six months later without any apparent cause (illness, poisoning) a marked decrease in water exchange occurred—in some animals diminishing to the pre-operative level. However, neither the specific gravity of the urines nor the concentrating ability of the kidneys increased. Food intake decreased only in those animals in which the water exchange returned to the pre-operative level. Nevertheless, even complete starvation at an earlier period did not cause such a marked decrease in polyuria (see de Bodo and Prescott). That the adenohypophyses were functioning normally was evidenced by 1) normal post-absorptive blood sugar level, 2) no hypersensitivity to insulin, 3) ability to withstand fasting for eight days, 4) no occurrence of spontaneous hypoglycemic crises.

The adrenals of these animals appeared perfectly normal in size and structure in contrast to those of our completely hypophysectomized dogs which showed marked atrophy of the cortex. On the other hand, the thyroids of the diabetes insipidus dogs were extremely small, but histologically normal having cuboidal epithelium, whereas the completely hypophysectomized animals had a thyroid of normal size but with flat epithelium.

These findings further reveal some participation of the thyroid gland in diabetes insipidus and are considered a compensatory effort

The water exchange of diabetes insipidus dogs under varying nutritional and hydration conditions RICHARD C DE BODO and KATHRYN F PRESCOTT (by invitation) *Dept of Pharmacology, New York Univ College of Medicine* (Read by title) In a series of dogs diabetes insipidus was produced by interruption of the supraoptic-hypophyseal tract Continuous kymographic records showed that two-thirds of the daily water intake and urine output occurred during the 12 hours following feeding, just as in normal dogs

The daily water exchange varied within different dogs from 3000-10,000 cc depending upon the amount of food ingested On fasting, with water given ad libitum, the water exchange decreased to about 1500-2000 cc on the first day, and never fell below 1000 cc even after eight days The specific gravity of the urines varied between 1.003-1.006 Normal dogs under similar conditions drank very little water and excreted a very small amount of concentrated urine

When the diabetes insipidus dogs were fed a diet of chopped meat but were deprived of water, they still excreted a fairly large amount of urine of specific gravity of 1.006-1.014 during the first 24 hours On the second day of water deprivation, most of the animals refused food, all excreted a small amount of urine of specific gravity of 1.010-1.028 and the freezing point of their blood sera decreased to about -90°C One of the animals died as a result of the experiment Normal dogs tolerated water deprivation for a much longer period, some animals taking food even after eight days All excreted a small amount of very concentrated urine and the freezing point of their sera never went below -67°C

Inhibitory responses of pregnant cat's uterus to epinephrin and hypogastric stimulation (Read by title) E C DEL POZO, *Dept of Physiology, Inst Politecnico Nacional, Mexico, D F* In the course of experiments intended to study the action of cocaine on pregnant uteri, it was observed that, in cats in the final stages of pregnancy, the uterus responded with inhibition to the injection of epinephrin and to the stimulation of the hypogastric nerves (centrally crushed)

Since this type of responses had not been reported before, to our knowledge, it was decided to study the reactivity of pregnant uteri at term to the mentioned types of stimulation The observation herein reported was confirmed in every uterus tested in the final stages of pregnancy

The inversion from inhibition to contraction first reported by Cushing in pregnant uterus of the cat (*J Physiol*, 35 1, 1906) seems to be related to the concentration of progesterone as shown by the

experiments of Kennard (*Am J Physiol*, 118 190, 1937) This inversion by progesterone had already been observed by Van Dyke and Gustavson (*J Pharmacol Exper Therap*, 37 379, 1929) On the other hand, it is thought (Reynolds, *Physiology of the Uterus*, New York, 1939) that the blood progesterone is reduced in the late stages of pregnancy, a fact which could explain our findings

Physiological actions of scorpion venom E C DEL POZO and G ANGUIANO L (by invitation) *Dept of Physiology, Inst Politecnico Nacional, Mexico, D F* Saline extracts of venom from ground telsons of *C. suffusus suffusus* were precipitated with acetone, dried, and then dissolved and injected into anesthetized cats

Poisoned animals showed fibrillary and clonic contractions of skeletal muscles, irregularity, increased amplitude, and then paralysis of respiratory movements, vasoconstriction, sialorrhea, pupillary dilation, and piloerection

The muscular effects are greatly attenuated by section of the motor nerves Maximal stimuli applied to a muscle through its nerve after venom injections produce contractions of greater amplitude and duration than normally After adequate doses, single shocks produce double peaked responses Tetani are obtained with relatively low frequencies These effects decrease with repetition of the stimuli, and reappear after a short rest period Decurarization is obtained when venom is administered after paralyzing doses of curare

High doses of venom block the muscular responses to nerve stimulation, but contractions are obtained with direct stimulation

The increased amplitude of respiratory movements is due to the muscular effects, as shown by records of the diaphragmatic contractions to phrenic stimulation That respiratory paralysis is due to central effects of the venom is shown by the fact that the diaphragm contracts when the phrenics are stimulated

Vasoconstriction is not observed after destruction of the spinal cord Denervation of the salivary glands abolishes almost entirely the salivary response to the venom

The simultaneous transport of T-1824 and radioactive red cells through the heart and lungs PHILIP DOW, P F HAHN* (by invitation), and W F HAMILTON, *Dept of Physiology, Univ of Ga School of Medicine, Augusta, and Dept of Pathology, Univ of Rochester School of Medicine and Dentistry* (*Now at Vanderbilt Univ School of Medicine) To test the objection that rapidly injected dye might leave a considerable residue on its first passage through the lungs and thus give falsely high estimates of its dilution for calculations of blood flow, the following experiment was done on dogs anesthetized with morphine and barbital Red cells tagged with radioactive iron, in plasma dyed

with T-1824 (1.6 mg), were rapidly injected into the superior vena cava. Immediately, a clamp on the aortic arch diverted the entire left ventricular output through a cannula into a series of test tubes presented in mechanically timed succession. These samples were measured and analyzed for dye and for radioactivity.

Recovery of neither cells nor dye was complete, probably because of total collapse of some vascular circuits with diminishing flow. The curves of concentration and recovery of radioactivity preceded those for the dye, indicating a more rapid transit of the cells in some part of the circuit. Otherwise the similarity of the curves furnishes no evidence of preferential retention of dye (at the concentration used) as compared with the cells.

Therefore, cardiac outputs obtained by the injection method should not be considered as erroneously high because of retention of dye in the lungs.

Relation of B vitamins, inanition and methionine to inactivation of estrone by liver. VICTOR A. DRILL and CARROLL A. PFFIFFER (by invitation). *Depts. of Pharmacology and Anatomy, Yale Univ. School of Medicine, New Haven.* Adult female rats were castrated and pellets of estrone, averaging 50 mgm, implanted in the spleen. Following control vaginal smears the animals were placed on a diet deficient in the whole vitamin B complex. Such animals failed to inactivate the estrone, as indicated by the vaginal smear, after 20 to 30 days. Paired control animals, receiving vitamin B complex, but limited to the amount of food consumed by the deficient animals each day, showed a similar result. A second experiment with other rats gave the same result.

In one experiment a third group of rats was included which was similar to the control inanition rats in all respects, but received in addition 50 mgm of methionine per day. They failed to inactivate estrone at the same time as the other groups. In a fourth study the food intake was limited to 3 grams per day, all animals receiving the whole vitamin B complex, and half of them 50 mgm of methionine per day. Such animals also failed to inactivate estrone, no difference being noted in the methionine fed rats.

It appears that a deficiency of the whole vitamin B complex affects the inactivation of estrogen only through the concomitant inanition produced. Supplements of methionine were without effect. [Support by grants from Fluid Research Fund, Yale Univ. Medical School, and Eli Lilly and Company.]

The respiratory and circulatory response of normal man to 100, 18, 16, 14, 12, 10 and 8% O₂. ROBERT D. DRIPPS (by invitation) and JULIUS H. COMROE, JR., *Dept. of Anesthesiology, Harrison Dept. of Surg. Research and Dept. of Pharmacology, Univ. of Penna.* The respiratory and circulator

responses of normal man to inhalation of low oxygen mixtures were measured in 60 subjects in an attempt to determine a) the magnitude of these responses and b) the threshold of the respiratory and circulatory systems to anoxia. The subjects breathed oxygen-nitrogen mixtures (21, 18, 16, 14, 12, 10, 8 and 100% O₂) for 8 minutes from Douglas bags or a demand system. Respiratory minute volume, pulse rate and arterial oxygen saturation (oximeter) were measured. To minimize the factor of spontaneous variation the increase in respiratory minute volume and pulse rate associated with low O₂ mixtures was compared to the immediate decrease in these figures when the subjects were suddenly changed from anoxic mixtures to 100% O₂. From the data thus obtained it is concluded that none of the subjects' respiratory or circulatory systems showed any measurable response to 18% O₂, while some subjects showed a slight but definite response to 16% O₂. This was particularly noticeable as far as pulse rate changes were concerned. No consistent increases in respiratory minute volume were noted until 10% O₂ was reached. Marked individual variations were seen, some subjects showing no response even to 10 or 8% O₂. In the course of these experiments we measured changes in respiratory minute volume when normal subjects breathed 100% O₂ after room air. No significant immediate change in breathing or pulse rate was observed, but at the end of 4-8 minutes definite respiratory stimulation occurred. It is concluded that the chemoreceptors are not tonically active in normal man breathing room air. [Work done under contract with the Office of Scientific Research and Development.]

The effect of continuous and of intermittent pressure breathing on kidney function. By D. R. DRURY, J. P. HENRY (by invitation), P. O. GREELEY, IRENE KLAIN (by invitation), and ELI MOVITT (by invitation), *From the Dept. of Aviation Medicine, School of Medicine, Univ. of Southern California, Los Angeles, California.* Continuous Pressure Breathing, especially in the range of 20 to 50 mm Hg positive pressure, exerts a definitely deleterious effect on the circulation. This is difficult to assay in quantitative terms. For such a test we have investigated the reduction in kidney function produced by pressure breathing. We find that using continuous pressure breathing there is increasing impairment of kidney function with increases in mask pressure. Then using kidney function as a method of assay, we compared the two types of pressure breathing, contrasting each level of continuous pressure breathing with the equivalent pressure needed for the intermittent method. The results indicate that there is an advantage in the use of the intermittent method.

The effects of explosive decompression on human subjects ABRAHAM EDELMANN, (by invi-

tation) W V WHITEHORN, (by invitation) and FRED A HITCHCOCK *Laby of Aviation Physiology and Medicine, The Ohio State Univ, Columbus* Human subjects have been subjected to explosive decompression (rapid reduction of the barometric pressure) at rates varying from 2 to 21 p s i per second This is equivalent to changing the simulated altitude from 8,000 to 35,000 feet in from 4 to 0.3 seconds In more than 1,000 experiments on upwards of 250 different subjects, no ill effects have resulted No changes were found in electrocardiograms, chest X-rays or audiograms Subjective symptoms were the rushing of air from the nose and mouth and a feeling of distension in the thorax and abdomen The incidence of severe gas pains was no greater than in control experiments in which the rate of decompression was about 3,000 feet per minute

In a series of experiments designed to test the effect of explosive decompression on the incidence of decompression sickness a significant increase was found when subjects were kept at altitude without exercise for one hour following the explosion However there was no significant difference between the incidence of the bends following explosive decompression and following decompression at 3,000 feet per minute when exercise or altitudes above 38,000 ft were used Thus, while explosive decompression may have a bends producing action, this effect seems to be masked by exercise or increased altitude

These data give no support to the concept of a sudden burst of nitrogen bubbles in the blood and tissue fluids as a result of explosive decompression [Work done under contract with the Office of Scientific Research and Development]

Studies in nerve degeneration and regeneration JOSEPH ERLANGER and GORDON M SCHOEFFLE *Dept of Physiology, Washington Univ School of Medicine, St Louis, Mo* The preparation used is the phrenic nerve with two of its roots of origin One is crushed, the fibers of the other, remaining intact, serve as the control Movable stimulating electrodes are applied to the nerve proper and fixed leads are taken from the roots separately Results are expressed as ratios,—degenerated or regenerated over normal $\times 100$ The first 3 cm are not available for observation

Degeneration is complete in 4 days After 3 days, excitability and conduction rate still are normal,—likewise in a 3 day 18 hour preparation At 3 days area ratios are much reduced, the more so the greater the distance of conduction These results are compatible with either abrupt failure at random loci or failure proceeding *centripetally* Data derived from the nerve trunk through observations on peripheralwards conduction are compatible with either random or centrifugal failure Pre-

sumably failure is abrupt at randomly scattered loci

Regeneration After 30 to 40 days excitability ratios at long distances are 5 or less, the normal being over 90 These ratios increase as the stimulator approaches the crush They increase also with regeneration time, and the relative slopes of the curves decrease Conduction rate ratios behave similarly Conduction rats vs excitability possibly plots a straight line, one not passing through the origin Area ratios from points just central to the lesions increase as the stimulator approaches the leads, the curves becoming approximately horizontal between 120 and 190 days, when conduction ratios still are small [Work done in part under contract between O.S.R.D. and Washington Univ]

A method of observing transient leucopenia HIRAM E ESSEX and ALFONSO GRANA¹ (by invitation) *Mayo Foundation Rochester, Minnesota* By means of a transparent chamber (Clark, Florey) inserted in the ears of rabbits, the behavior of the leucocytes can be observed in the newly formed blood vessels In response to intravenous injections of appropriate doses of glycogen, gum acacia, extracts of *Ascaris suum* and fluid from hydatid cysts, the majority of the leucocytes cease to move along the walls of the veins in one to two minutes The leucocytes adhere to the walls of the vessels and to each other, thus frequently forming clumps containing as many as four or five cells The cells usually resume their normal behavior in fifteen to thirty minutes

If the number of leucocytes was determined during the period of their altered behavior, a marked leucopenia was observed in blood taken from an ear or leg vein The most profound leucopenia coincided with the period when the majority of the cells were adherent to the walls of the veins of the ear This fact suggests that the phenomenon is a general one

Injections of glucose, horse serum, or normal saline did not alter the behavior of the leucocytes

The influence of other materials and of anaphylaxis on the behavior of the leucocytes is being investigated Also experiments are in progress to determine whether chronic leucopenia can be produced by prolonged administration of certain materials

Effects of frostbite on the minute blood vessels of a peripheral vascular bed HIRAM E ESSEX and RAMON QUINTANILLA (by invitation) *The Mayo Foundation Rochester, Minnesota* It has been thought that frostbite results in coagulation of the blood in the smaller vessels and eventual anoxia which causes further destruction of the frost bitten tissue To investigate this question we made use of

¹ Guggenheim Fellow (From the Institute of Experimental Medicine Montevideo Uruguay)

the Florey modification of the Clark transparent chamber inserted into the ears of rabbits. Pieces of CO_2 ice were applied directly to the window for thirty seconds. The vessels that had grown into the chamber were completely frozen. Immediately after thawing, the vessels appeared normal in every respect. However, after five or ten minutes it was apparent that serious injury had been done. The vessels dilated widely and became filled with red and white blood cells. The permeability of the vessel walls increased, the plasma was drained from the vessels and the formed elements were left concentrated in the vessels in conglomerate masses which were not owing to coagulation since an identical picture was seen in the vessels of animals whose blood had been made incoagulable by injections of heparin (Motion picture)

Anticonvulsant action of drugs against metrazol and anti-epileptic activity. GUY M. EVFRET (introduced by R. K. Richards) *Dept of Pharmacology, Abbott Labs., North Chicago, Ill.* Out of a group of 50 compounds tested as anticonvulsants, five which were highly protective in non-sedative doses against Metrazol convulsions in mice, cats, and dogs, have been distributed for clinical trial in epilepsy.

The table summarizes the preliminary evaluation of these drugs

Drug	Protective dose against metrazol (mg/kg)	Clinical evaluation	
		Grand mal	Petit mal
Oxazolindione 2,4 dione			
3,5 dimethyl	500	?	++
3,5,5 trimethyl (Tridione)	500	+	+++
3,5 dimethyl-5 ethyl	250	?	++
Barbituric Acid			
1,5,5-Trimethyl	100	+	-
5,5-diethyl-1 methyl	50	++	-
Phenobarbital	50	+++	-

On the basis of these results, it may be concluded that the anticonvulsant action of these drugs against Metrazol has given a useful index of anti-epileptic activity but does not differentiate between drugs effective in grand mal or petit mal.

Cerebral metabolism of hyperthyroid, thyroid-deficient and cretinous rats. J. F. FAZEKAS (introduced by E. B. Astwood) *From the Dept of Medicine, Tufts Medical School and the Joseph H. Pratt Diagnostic Hospital, Boston.* The oxygen consumption of minced cerebral cortex of normal, hyperthyroid and thyroid deficient rats was compared. The tissue was suspended in a saline phosphate medium, with glucose as the substrate and the oxygen consumption determined in the Warburg Apparatus. Triplicate observations were

made on each brain studied and the tissue was examined as soon as possible after excision. Hyperthyroidism was induced by feeding one per cent thyroxin supplemented with adequate yeast to prevent avitaminosis. Thyroid deficiency was induced by feeding 0.05% propylthiouracil. Cretinism was induced by feeding 0.1% propylthiouracil in the diet to the lactating mothers. One half of each litter, treated with 1 mg of thyroxin daily, grew normally and served as controls.

Thirty-six observations on twelve rats, 21 to 28 days of age, six cretins and six litter mate controls, disclosed an average difference in oxygen consumption of only 7.8%. Eighteen observations on three hyperthyroid and three thyroid-deficient animals treated with 0.05% propylthiouracil for nine months revealed an average difference of 5.9%. In both groups of experiments the oxygen consumption of the cortex was slightly reduced in the hypothyroid animals. This slight and questionably significant reduction in oxygen consumption does not reflect the sluggish behavior nor explain the tolerance to anoxia of these hypothyroid animals.

A new method of representing alveolar air concentrations at altitude. W. O. FENN, L. E. CHADWICK, H. RAHN, and A. B. OTIS (by invitation) *Dept of Physiology, School of Medicine and Dentistry, Univ of Rochester, Rochester, New York.* If the alveolar tensions of CO_2 are plotted as ordinates against the tensions of oxygen as abscissae a diagram is obtained in which each altitude is represented by a straight line of negative slope. When pure O_2 is breathed the slope of this line is always -1 and a decrease of alveolar pCO_2 caused by increased ventilation or by any other means must result in a corresponding increase of pO_2 . When air is inhaled the slope of the altitude diagonal varies with the R/Q but the abscissa at $\text{pCO}_2 = 0$ is the same. The beneficial effect of adding CO_2 to the inhaled air is easily demonstrated. The gain in oxygen tension due to hyperventilation is shown to be due (1) to the decrease in pCO_2 and (2) to the increased R/Q or added CO_2 , which permits more pO_2 for the same degree of acapnia. Families of curves representing arterial oxygen saturation, cardiac output (for a given venous O_2 saturation) and venous O_2 saturation, (for a given cardiac output) can also be included. The diagram shows that overventilation would be advantageous so far as the transport of gases is concerned so long as the arterial saturation is below about 90%. The amount of alveolar ventilation required for any altitude or pCO_2 or pO_2 can be calculated for a given oxygen consumption. A line representing the average alveolar air composition at altitude can be drawn, as well as curves indicating the range of alveolar air compositions which are consistent with normal performance or abnormalities of varying degrees. On a larger scale the areas

of deterioration due to too much or too little CO_2 or O_2 can be indicated [Work done under contract with the Office of Scientific Research and Development]

The effect of age on the hypoglycemic depletion of glycogen in the central nervous system SHIRLEY FERRIS (by invitation) and HAROLD E. HIRWICH Dept of Physiology and Pharmacology, Albany Medical College, Union Univ., Albany, New York. Previous work from this laboratory shows that hypoglycemia produces a decrease in the glycogen of the central nervous system of the adult dog in such a way that the higher anatomic and newer phyletic layers suffer the greater depletions. In the present investigation the effects of hypoglycemia upon the glycogen content of the various portions in the central nervous system of newborn and 6½ weeks old kittens were determined. All animals received two units of standard insulin per kilogram of body weight every hour until the conclusion of the experiment. Sodium iodoacetate was used to fix brain glycogen *in situ* and the glycogen was determined according to Kerr's method. In the newborn animal the more caudal parts showed the greater fall in concentration: the spinal cord was depleted most, followed in order by the cerebellum, medulla, thalamus and corpora quadrigemina, while the cerebral cortex did not show a significant fall. In the 5-8 week old kittens, only the higher parts exhibited significant decreases. The glycogen in the cerebral cortex was depleted to the greatest extent, followed by the corpora quadrigemina and thalamus, while the concentrations in the cerebellum, medulla oblongata and cord were not changed significantly during hypoglycemia. This pattern of glycogen depletion is intermediate between that of the adult and the newborn: the higher areas suffer smaller impairments than in the adult, while the older phyletic regions are not depleted and in this way differ from the newborn. [This study was aided by a grant from the Scottish Rite Fund.]

The role of intra and extracellular cH in neuro-humoral stimulation JOHN C. FINERTY (by invitation) and ROBERT GESELL Univ. of Michigan. Striated muscle is classified as cholinergic by Dale and associates. Acetylcholine is considered highly electrogenic by Nachmansohn and associates, and humoral stimulation of muscle is known to occur through intermediation of myoneural junctions (Buchthal and Linhard). These facts support the humorelectrotonic theory which holds that electrotonic currents set up at myoneural junctions stimulate in proportion to the strength and duration of the currents and the excitability of the muscle fibers.

The stimulatory action of extraneous acetylcholine on respiratory muscle was potentiated in an acid medium, presumably through the anti-

cholinesterase activity of acid, locomotor muscles, however, were found less responsive in acid environment. To explain this apparent contradiction to the acid humoral concept, the role of intra and extracellular cH was examined. Jacobs has shown that differential penetration of carbon dioxide and sodium bicarbonate allows selective control of intracellular and extracellular acidity. Carbon dioxide, which increases intra and extracellular cH, increased the intensity and duration of action potentials of the rectus abdominus but decreased the frequency and duration of potentials of the sartorius. When carbon dioxide and sodium bicarbonate were added to the ambient solution so that the external cH was kept constant, the sartorius response was potentiated like that of respiratory muscles.

These findings suggest that acid acts as an anti-cholinesterase within end plates where acetylcholine is liberated and that extracellularly it depresses the excitability of muscle fiber to electrotonic excitatory current.

Changes in muscle proteins during atrophies of various types and the retardation of some of these changes by electrical treatment ERNEST FISCHER and VIRGINIA W. RAMSEY (by invitation) Baruch Center of Physical Medicine, Medical College of Virginia, Richmond. Total protein concentration in rabbit gastrocnemius diminishes about 14% during denervation atrophy of 22 to 30 days duration. In atrophy due to tenotomy or due to immobilization by cast, the weight loss is practically the same as after denervation. However, the total protein loss is the same only for tenotomy, while during immobilization the protein loss is only about ½ of the loss in the other atrophies. Collagen concentration increases in all three types of atrophy about reciprocally with the weight loss, but this relative increase is somewhat less than expected under the assumption that the collagen present in the whole muscle remains constant. Non-collagenous protein is decreased by 13, 25 and 29% by immobilization, tenotomy, and denervation respectively. Precipitable myosin is diminished only by 11% for immobilization, but 69 and 78% for tenotomy and denervation. The hydrophilic power of the muscle mash is increased by about 35% for immobilization and denervation, but is decreased by about 13% for tenotomy.

Daily electrical treatment of denervated muscles is effective in retarding weight loss and deterioration of muscle protein. Treatment applied to a leg in a limb position, so that the muscle contracts against high resistance during stimulation, is much more effective than treatment in a position, in which the muscle contracts freely against no or little resistance.

The oxygen consumption concerned with growth in *E. coli* and the effect of sulfathiazole and N-

propyl carbamate on it KENNETH C FISHER and FORENCE H ARMSTRONG (by invitation) *Univ of Toronto* The consumption of oxygen by growing cultures of *E coli* has been measured From simultaneous observations on oxygen consumption and growth it was found that the concentration of sulfathiazole and n-propyl carbamate which are just sufficient to stop growth completely, lower the rate of oxygen consumption but leave intact approximately 45% of the normal rate

In a number of experiments the cultures in the respirometer vessels were permitted to exhaust the nitrogen source From the moment this occurs the rate of oxygen consumption falls rapidly until, after approximately one hour, it reaches a comparatively stable value which is about 45% of that existing immediately prior to the exhaustion of the nitrogen source It thus appears that approximately 55% of the oxygen consumption of the growing cell is concerned with the uptake of the nitrogen source, i.e. with growth

Concentrations of sulfathiazole or n-propyl carbamate up to those which stop growth completely have little or no ability to depress the stable respiration established after growth ceases However the inhibition by these two substances of the extra oxygen consumption seen when the cells are actively growing, closely parallels the concomitant inhibition of growth [Supported by a grant from the John and Mary R Markle Foundation of New York]

Effect of thyroxin on estrogen-induced changes in fowl WALTER FLEISCHMANN *Dept of Pediatrics, Johns Hopkins School of Medicine* Thyroxin, when administered simultaneously and in equal amounts with estradiol dipropionate in immature chicks neutralizes the ability of the estrogen to increase serum calcium, inorganic phosphorus, lipid phosphorus, protein phosphorus and cholesterol, but does not inhibit the growth of the oviduct (Fleischmann and Fried, *Fed Proc* 3 10, 1944, *Endocrinology* 36 406, 1945) In pigeons thyroxin was observed to inhibit estrogen-induced changes in the plasma levels of calcium, neutral fat and all phosphorus fractions, without inhibiting the action of estrogen on the formation of endosteal bone and promotion of the growth of the oviduct (McDonald, Riddle and Smith, *Endocrinology* 37 23, 1945)

In the Brown Leghorn capon thyroxin injected simultaneously and in equal amounts with estradiol dipropionate has no effect on the salmon coloring induced by estrogen in the black breast feathers The salmon bar produced by injecting 0.5 mgm estradiol dipropionate on three subsequent days is not modified by simultaneous injection of 1 mg thyroxin These studies indicate that the inhibiting effect of thyroxin is confined to metabolic changes, whereas the structural changes brought about by estrogen are not affected

Experiments are in progress to determine the mechanism of this effect of thyroxin Thyroxin does not diminish the phospholipid content of the liver in chicks Dinitrophenol has no inhibiting effect on the hypercholesterolemia produced by estrogen [Aided by a grant from the Commonwealth Fund The hormones were kindly supplied by Roche-Organon, Inc., Nutley, N. J.]

The effect of insulin on blood cocarboxylase PIERO P FOA, JAMES A SMITH (by invitation) and H WEINSTEIN (by invitation) *Dept of Physiology and Pharmacology, Chicago Medical School* Evidence is available indicating that insulin influences the metabolism of phosphate in relation to the metabolism of carbohydrate The present work deals with the influence of insulin on the phosphorylation of thiamine When thiamine (1 mg or 10 mg/kg) is injected intravenously into a normal dog, anesthetized with ether or unanesthetized, blood cocarboxylase rises from 5-10 γ /100 cc to a peak of about 100 γ /100 cc in about 15 minutes and then gradually returns to normal The concentration of inorganic phosphate does not change significantly, probably because the amount used in the phosphorylation of thiamine is very small relative to the total amount present If larger doses (100 mg/kg) of thiamine are injected a significant drop in inorganic phosphate can be detected, but such doses are very toxic The concentration of glucose does not change significantly, except when ether is administered A rise in blood cocarboxylase (2-3 times the basal value) with a simultaneous drop in inorganic phosphate follows the injection of 1 or 10 units of insulin/kg This phenomenon is more marked if the basal concentration of cocarboxylase had been previously increased by daily intramuscular injections of thiamine Depancreatized dogs have little (2-3 γ /100 cc) cocarboxylase in the blood and its concentration does not rise following the injection of thiamine, unless insulin is injected These results are consistent with the hypothesis that insulin is necessary for the phosphorylation and, therefore, for the utilization of thiamine

Depression of the cerebral cortex induced by applications of acetylcholine FRANCIS M FORSTER, WINSLOW J BORKOWSKI and ROBERT H McCARTER (introduced by M H F Friedman) *Dept of Neurology, Jefferson Medical College, Philadelphia, Pa* The local application of acetylcholine to the exposed cerebral cortex of the cat produces a period of depression of electrical activity followed by acetylcholine discharges The depression of activity is independent of systemic effects of acetylcholine The depression of activity is accompanied by decrease in cortical function, as determined by motor and acoustic responses and by strychnine-induced activity The depression of electrical activity spreads over the cortex, and

apparently not along neuronal pathways but in all probability in linear fashion. Depression appears in distant areas in which the acetylcholine discharges do not appear.

This type of cortical depression is not due to stimulation of suppressor areas, nor to mechanical stimulation.

The relationship in the hand between total heat exchange and blood flow at various ambient temperatures. FORSTER, R. E., II, FERRIS, B. G., JR., and DAY, R. L. (introduced by H. C. Bazett). *The Quartermaster Corps Climatic Research Lab., Lawrence, Mass.* At the Quartermaster Corps Climatic Research Laboratory, the thermal exchange and blood flow in the hands of two lightly clad, healthy young men were measured at a variety of ambient temperatures in a combined "Plethysmocalorimeter." The calorimeter was modeled after that of Hardy and Day for infants. Blood flow was measured using the instrument as a plethysmograph in conjunction with the venous occlusion method of Brodie.

The temperature drop per cubic centimeter of blood, calculated from the blood flow and heat loss in the hand per unit time, revealed extremely low values. Either the arterial blood was cooled considerably, prior to its entry into the hand at the wrist, or else the venous temperature was higher than the skin temperature, or perhaps both. This was true to a degree not appreciated by those who have used the calorimeter to measure peripheral blood flow. The arguments in favour of the hypothesis of the pre-cooling of arterial blood by the returning venous blood are presented. Several measurements of the temperature of arterial and venous blood were taken under identical conditions and corroborated this view. After prolonged exposure, blood flow as low as 0.2 cubic centimeters per hundred cubic centimeters of tissue per minute were obtained. The evaporative heat loss represented the majority of the total heat loss at either extreme of the range, 15-37°C. The overloading of the body heat exchange mechanism at both extremes of the same range was also demonstrated.

Renal function in the rabbit as influenced by the administration of water, anesthetics and diuretics. R. P. FORSTER (by invitation) and J. P. MAES. *Dept. of Zoology, Dartmouth College, and the Dept. of Physiological Sciences, Dartmouth Medical School.* In this series of 46 experiments on 41 rabbits 368 clearance periods were studied in which the creatinine clearance was used to estimate the glomerular filtration rate, the para amino hippuric acid clearance for the effective renal plasma flow, and the glucose T_m for the number of functioning glomeruli. After it was found that these values were unaffected by the animal's position during the experiment (standing, prone, or supine), and rabbits were loosely restrained in a supine position

while urine samples were collected at measured intervals by in-lying catheter, and blood samples were obtained from the central ear artery or sometimes from the ventricle.

Untrained rabbits typically maintained constant renal functional values for 3 or 4 hours with this treatment. Well hydrated rabbits of 2.5 or 3 kilogram body weight had glomerular filtration rates of approximately 15 ml per minute and renal plasma flows of approximately 50 ml per minute while being infused at the rate of 0.6 ml per minute.

Diuresis resulting from the administration of 100-200 ml of tepid water by stomach tube was associated with increases in the rate of glomerular filtration, the renal plasma flow, and the glucose T_m .

The administration of ether was followed by reductions in the glomerular filtration rate and the renal plasma flow, while sodium pentobarbital injected intravenously (30 mg/kg) did not affect these values.

Intravenous injections of mannitol and theophylline resulted in marked diuresis without affecting the filtration rate or the renal plasma flow.

Changes in postural steadiness and pulse rate after short vigorous exertion. JOSEPH C. FRANKLIN, HAROLD GUETZKOW and JOSEF BROZEK (introduced by Ancel Keys). *Lab. of Physiological Hygiene, Univ. of Minnesota, Minneapolis, Minnesota.* (Read by title.) Pulse rates were taken with subjects standing, before each one-minute steadiness (ataxiometer) measurement. After resting (control) data were obtained, 12 subjects ran on a treadmill for three minutes at seven miles per hour at grades varying from 7.5 to 10% climb according to individual "fitness." Pulse and steadiness were determined at the 1st, 5th, and 11th minute after running. In six men steadiness was measured with eyes open on the first day and with eyes closed on the second day, the order was reversed for the other six.

Pulse rate rose from a resting average of 80 beats (100%) to 148 (184%) immediately after run fell to 105 (131%) at the 5th minute and showed no further recovery at the 11th minute. Control scores for total body sway, in centimeters per minute, were 9.6 with eyes open and 15.7 with eyes closed. At the 1st, 5th, and 11th minute after running, body sway with eyes open was, respectively, 24.3, 15.9, 11.7 cms or 254, 166, 122% of normal, with eyes closed 37.2, 28.9, 21.9 cms or 237, 184, and 140% respectively.

The data show that, in the early part of recovery, postural steadiness was more sensitive to the "stress" of running than was the pulse rate. Body sway, in centimeters, in rest and after exercise was smaller with eyes open than with eyes closed. Steadiness scores obtained at the 5th and the 11th

minute of recovery were significantly closer to normal with eyes open than with eyes closed

Experimental production of uremia in dogs by protein depletion SMITH FREEMAN, TSAN-WI N LI (by invitation) and CHI CHU WANG (by invitation) *Dept of Physiology, Northwestern Univ Medical School, Chicago* Dogs weighing approximately 15 kg were fed daily a protein-deficient diet of the following composition: rice 230 grams, sugar 60 grams, lard 30 grams, yeast 15 grams, salt 8 grams, and 2 drops of percomorph oil. Three times weekly the animals were subjected to plasmapheresis (10 cc of blood per kg body weight was removed each time). These animals show an increase in the serum inorganic phosphorus and non-protein nitrogen after 3 or 4 weeks of depletion. Anorexia, weight loss, scanty urine and a marked elevation of the serum N P N and inorganic phosphorus develop rapidly. Protein and granular casts appear in the urine. The serum albumin decreases while free and total cholesterol were little altered by this procedure. The Rose Bengal dye clearance and serum phosphatase both decreased.

Autopsy findings included pale soft kidneys with numerous grayish-white areas scattered throughout the cortex. Microscopic examination of kidney sections revealed extensive tubular injury as well as other evidences of kidney damage.

Physiologic icterus of the newborn By L WILLARD FREEMAN, ARTHUR LOEWY (by invitation), and VICTOR JOHNSON *From the Dept of Physiology, The Univ of Chicago* Elevated serum bilirubin levels can be demonstrated in infants by the fifth day of life. Johnson and Freeman have demonstrated the presence of free fatty acids and soaps in the chyle and serum of animals and in the serum of humans following the ingestion of fat. The amounts found were sufficient to account for the hemolysis observed under the test conditions. Compared to a short time after birth, the infant is born with a relative polycythemia. The newborn infant is exposed to a fat diet which is high compared to the levels to which it is exposed while still attached to the maternal circulation. To test the possible role of fat in the early destruction of erythrocytes, umbilical cord blood was obtained from fifty newborn infants. These infants were then placed on formulae with various fat contents. The control group on standard formula (3.6% fat) showed serum bilirubin levels of 1.36 milligrams per cent at birth and 5.41 milligrams per cent on the fifth day. The group on reduced fat intake (1.8% fat) had similar control levels and 4.21 milligrams per cent on the fifth day. The group on practically fat-free diet (0.03% fat) with similar control levels had 3.09 milligrams per cent. These results would indicate that the ingestion of fat plays an important role in the destruction of erythrocytes in the newborn infant and consequently in the production of icterus.

The influence on gastric secretion of fluids introduced into the intestine M H F FRIEDMAN, I J PINCUS (by invitation) and J EARL THOMAS *Dept of Physiology, Jefferson Medical College, Philadelphia, Pa* The experiments were performed on three dogs with Pavlov pouches, one dog with a Heidenhain pouch and three dogs with gastric fistulas. Each animal also was provided with an intestinal fistula.

Intestinal instillation of 60 to 850 cc of water, physiological saline or 0.1 N HCl resulted in an increase in volume of gastric secretion only when the gastric glands were already excited by food, insulin or histamine. These fluids were without immediate or delayed effects when the gastric glands were at rest. The increase, when it occurred, developed only after the actual intestinal inflow of fluid had ended, suggesting inhibitory influences from the intestine due possibly to mechanical distension. If histamine injections were maintained for four hours the excess juice secreted by the gastric glands of the pouch and stomach was always proportional and frequently equal to the volume of fluid introduced into the intestine. Due to technical difficulties a similar balance between the volumes of fluid instilled into the intestine and secreted by the gastric glands could not be verified in feeding experiments.

As previously reported, gastric secretion when stimulated by food or insulin but not when stimulated by histamine was inhibited if the pH of the intestinal contents was depressed below 2.5 by intestinal infusion of 0.15 N HCl. Following inhibition the secretion was increased to above control levels. We found that the extent of increase was related to the volume of fluid introduced and not to the degree of preceding inhibition.

Color changes in the mucosa of the colon in children as affected by food and psychic stimuli M H F FRIEDMAN and WM J SNAPE (by invitation) *Dept of Physiology, Jefferson Medical College, Philadelphia, Pa* (Read by title) In each of three children, ages 4, 9, and 10 years, there was at the site of a colostomy a large rosette of everted mucous membrane of the colon. The colostomies had been established 3 to 9 months previous to these studies for the purpose of surgical correction of anorectal deformities. In none was pathological change found associated with the colon. The children were in excellent health.

Changes in the color of the mucosa were noted by direct inspection and matching with color standards of a hemoglobin scale (Tollquist type). Observations were made on the recumbent subject 16 to 18 hours after the previous meal.

Mildly painful stimuli applied to the abdomen in the region of the colostomy resulted in immediate blanching of the mucosa. Normal color returned within 10 minutes. In some instances the blanching was followed by reddening. The mere verbal sugges-

tion of pain also produced immediate blanching. Discussion of unpleasant past experiences also gave rise to mucosal blanching.

Sight or smell of appetizing foods resulted in marked reddening and engorgement of the mucosa. During the act of eating the mucosa remained engorged but returned to normal color after the meal was eaten. In one subject a transitory blanching preceded the intense engorgement. Food which was distasteful to one subject had only a slight effect on the color.

During the process of stool extrusion through the colostomy the mucosa remained pale but became markedly engorged after the stool was passed.

A practical criterion for evaluating the danger of explosive decompression. A. P. GAGGE and H. M. SWEENEY, *Aero Medical Lab., Air Technical Service Command, Wright Field, Dayton, Ohio*. Recent experiments¹ have shown that the relative expansion of internal gases, as a result of the decompression, and the time of the decompression itself, are the two most significant factors in setting up a criterion for evaluating the danger of explosive decompression to flying personnel. For an aircraft of cabin volume V (in cu ft) and cabin pressure P_c (in lbs/sq in) flying in an ambient pressure P_a (in lbs/sq in), it can be shown that danger for flying personnel may exist when

$$(P_c - 0.91)/(P_a - 0.91)$$

is less than

$$2.1 + 3.8 (V/A) \sqrt{(P_c - P_a)/P_a}$$

where A (in sq ft) is the area of the orifice causing the explosive decompression. The reliability of this criterion will be discussed in the light of current experimental data on human subjects.

Oxygen and carbon dioxide tensions in arterial blood and alveolar air at rest and after exercise in healthy subjects and in patients exposed to phosgene. MORTON GALDSTON and JOHN A. LUETSCHER, JR (introduced by Jay Tepperman), *Clinical Research Section, Medical Division, CWS, E. A. and Department of Medicine, Johns Hopkins Hospital, Baltimore, Md*. Direct determinations of pO_2 and pCO_2 in arterial blood (R. L. Riley, *Fed Proc* 4: 59, 1945) and in alveolar air were compared. Alveolar air samples were collected toward completion of blood withdrawal as follows: resting, end-expiratory, post-exercise, end-inspiratory. Blood was almost always withdrawn within one minute post-exercise.

In 15 comparisons (12 healthy, resting subjects) alveolar air pO_2 averaged 97 mm Hg and arterial blood pO_2 averaged 96 mm Hg. Decrease from alveolar to arterial pO_2 averaged 1 mm Hg. In 4 comparisons (4 healthy subjects, post-exercise)

alveolar air pO_2 ranged from 110 to 125, average 117 mm; arterial blood pO_2 ranged from 103 to 123, average 111 mm.

Comparisons were performed in 10 patients with recent acute or chronic inhalation of phosgene. In 14 comparisons (8 patients, resting) alveolar air and arterial blood pO_2 averaged 94 mm. In 5 comparisons (2 patients, resting) alveolar air pO_2 averaged 113, arterial blood pO_2 , 96, average decrease, 17 mm. In 5 comparisons (5 patients, post-exercise), alveolar air pO_2 averaged 121, arterial blood pO_2 , 118. In 4 comparisons (3 patients, post-exercise) alveolar pO_2 averaged 119, arterial blood pO_2 , 105 mm. Discrepancies between alveolar air and arterial blood pO_2 were consistent with other pulmonary function study results.

Average alveolar air and arterial blood pCO_2 values in healthy subjects, and patients ranged from 39 to 42 mm Hg, indicating true alveolar air samples were collected. Difficulties with direct determination of pCO_2 sometimes prevented precise comparison between alveolar air and arterial blood pCO_2 .

Sensitivity to morphine during recovery from hemorrhagic shock. SAMUEL GELFAN, *Dept of Physiology, College of Physicians and Surgeons, Columbia Univ*. Dogs recovering from deep hemorrhagic shock succumb to 25 mgs per kilogram of morphine given intravenously 24 hours or more after restoration of the blood volume. This dose which causes extreme circulatory depression in the animals recovering from shock is about $1/10$ of the minimal fatal intravenous dose for normal unanesthetized dogs. Only the animals whose blood volume reduction was sufficient to cause death unless the blood loss was restored by transfusion of blood or plasma exhibited this sensitivity. Dogs that had suffered large hemorrhages, and in some cases also sciatic stimulation for six hours, (see Wang, et al, 1945) and survived without replacement of lost blood could cope with the stress as represented by this dose of morphine, even though their blood volume was not restored.

These observations suggest the possibility that the vasomotor system, damaged during the period of critically reduced blood volume, remains unstable for some time after the restoration of the blood volume. The response to morphine may be considered a crude index of the rate of rehabilitation of dogs recovering from shock. [Work done under contract with the Office of Scientific Research and Development.]

Water intoxication and the electroencephalogram. E. GELLHORN¹ and H. M. BALLIN (by invitation), *Laby of Neuropsychology, Dept of Physiology, Univ of Minnesota, Minneapolis* (read title). Intraperitoneal injection of 5 per cent at intervals of 30 minutes leads to acute

¹ Sweeney, H. M. and M. H.
4: 69, 1945

Proceedings

² Captain, MC, AUS

toxication in rats which is characterized by the following changes in the electroencephalogram (1) Slow waves of a frequency of 1 to 3 per second and of an amplitude of 100 to 300 microvolts appearing singly or in groups to an increasing degree with progressing water intoxication (2) Convulsive potentials either as single or multiple spikes or in combination with slow waves similar to the pattern described by Gibbs as *petit mal* and "*petit mal variant*" respectively The various types of convulsive and slow potentials occur in the same animal at different stages of water intoxication In general, slow potentials precede convulsive spikes in time In animals treated with desoxycorticosterone the E E G changes consist largely of slow waves It is suggested on the basis of these findings that the different forms of the E E G observed in *petit mal*, *grand mal*, and *psychomotor seizures* are due to the same basic disturbances in brain function since similar changes in the E E G may be induced by the clearly defined experimental condition of water intoxication Water intoxication is accompanied by a reversible decrease in heart rate The changes in E E G and heart rate are not due to a fall in temperature since the latter was prevented by the application of external heat

Electromyographic observations under conditions of stimulation of the motor cortex ERNST GELLHORN and JAMES F BOSMA (by invitation) *Laby of Neurophysiology, Dept of Physiology, Univ of Minnesota, Minneapolis* Experiments were performed on the effect of stimulation of the motor cortex of cats and monkeys on muscular coordination by means of electromyograms Results were as follows (1) Very weak stimulation of the motor cortex causes relaxation of flexor and/or extensor muscle if a pre-stimulatory tonic activity is demonstrable in the electromyograms Such cortically induced inhibition is frequently followed by a post-stimulatory rebound (2) With slightly increased intensity which calls forth a movement (flexion or extension) reciprocal innervation of agonist and antagonist may be observed whereas somewhat stronger stimuli cause simultaneous activity in flexor and extensor muscle, i e co-innervation and, consequently, co-contraction during flexion or extension (3) Variations in the duration of the period of stimulation exert effects similar to those seen in experiments involving different intensities Whereas reciprocal innervation appears during the early phase of stimulation it is later followed by co-innervation while the stimulation continues (4) An inhibitory period frequently precedes and follows the period of stimulation These phenomena are interpreted as indicating that with increasing number of discharging neurons the peripheral effect on individual muscles changes from inhibition to excitation, and in the case of an antagonistic pair of muscles, from

inhibition to reciprocal innervation, and finally to co-innervation Under conditions permitting of facilitation the predominant type of coordination of fore- and hindleg muscles in flexor and extensor movements of moderate intensity is that of co-innervation

Decline in the rates of sweating of men working in severe heat S D GERKING (by invitation) and SID ROBINSON *Dept of Physiology, Indiana Univ, Bloomington, Ind* The hourly rates of sweating of men walking on a treadmill in severely hot environments declined steadily during the course of six-hour experiments The men were well acclimatized to the heat and maintained water balance by drinking 0.1 per cent saline in the experiments In fifty experiments the average rate of sweating during the first two hours, i e, initial rate, was 1400 grams/hr, and the sweating rates of the men declined from 10 to 80 per cent of this value by the sixth hour, depending upon environmental conditions The decrease occurred only in relatively high rates of sweating since the men were able to sweat at a practically constant rate (about 750 grams/hr) while working in moderate heat The declines of the sweating rates were distinctly greater in humid than in dry environments where the initial rate of sweating were about equal Also, in both humid and dry environments the decline was greater when the men wore Army jungle uniforms than when they wore only broadcloth shorts Another interesting response shown by men wearing clothing is that there was a greater decrease in their rates of sweating as the initial sweating rates increased Since the decline in sweating was not associated with dehydration nor with a decreased strength of the stimulus for sweating, it is concluded that the sweating mechanism was fatigued in some way In many experiments the men's body temperatures were increasing during the most rapid decline in their sweating (Robinson and Gerking, *Proceedings, Am Physiol Soc*, in Press) [*This work was done under a contract with the Office of Scientific Research and Development*]

Further observations on humoro-electrotonic nature of stimulation, inhibition, summation and after-discharge of nerve cells. ROBERT GESELL, E T HANSEN (by invitation), and JEANE SISKEL (by invitation) *Univ of Michigan* The humoro-electrotonic theory, which postulates that activity of nerve cells varies with the intensity of their electrotonic currents, was re-examined Continuous faradic stimulation of inspiratory afferents was found to produce inspiratory tetanus of progressively increasing intensity Similar stimulation of expiratory afferents produced comparable expiratory tetanus Such temporal summation of stimuli suggests progressive accumulation of acetylcholine at excitatory poles of neurons and an associated increase of excitatory electrotonic current Periodi-

cally interrupted stimulation produced step like increase of tetanus indicating step like accumulation of neurohumor

Selective stimulation of inhibitory fibers of Hering's nerve produced progressive reduction of tidal air. Such temporal summation of inhibition suggests accumulation of acetylcholine at inhibitory poles.

Reflex inhibition and reflex stimulation produced after discharges lasting several minutes. Double Hering nerve block produced a very gradual reduction of breathing. These findings suggest first, a slow destruction of acetylcholine at excitatory and inhibitory poles and second, that the respiratory center functions normally on impulses dating several minutes into the past.

Spatial summation of excitatory stimuli resulted from bilateral Hering nerve stimulation. Comparable spatial summation of inhibitory stimuli resulted from bilateral stimulation of inhibitory intensity.

Fitting theoretical counter E.M.F. of reflex inhibition against theoretical excitatory E.M.F. of reflex stimulation produced expected resultant diminution of breathing.

Volume flow of blood through the brain of man at rest, during hyperventilation and while breathing high CO_2 . FREDERIC A. GIBBS, HARRY P. MAXWELL (by invitation) and ERNA L. GIBBS (by invitation) (with the technical assistance of Ruth E. Hurwitz) *Univ. of Illinois, College of Medicine*. By injecting a suitable substance at a constant rate into an artery supplying the brain and determining its concentration in the returning venous stream, it is possible to estimate the cerebral blood flow (F. A. Gibbs). In the present study an 0.2% solution of Evans Blue (T-1824) was injected into the right internal carotid artery of seven patients at a rate of one ml. per minute. Blood samples were drawn from the right internal jugular with and without occlusion of the left internal jugular vein while simultaneous arterial samples were obtained from the femoral artery. The rate of injection and the difference in concentration of dye in the arterial and venous samples gave the necessary information for estimating the cerebral blood flow. With this value and the arterio-venous difference for oxygen it was possible to estimate oxygen consumption.

The method was checked in one case against direct volumetric determinations of cerebral blood flow. A large cannula was inserted into the right internal jugular vein and the left internal jugular vein was temporarily ligated, the cerebral venous return thus deflected through the right internal jugular was collected in a graduate. The methods checked to within 3%.

The average resting minute volume flow was 617 ml. per minute. The average oxygen consumption

was 39.2 ml. per minute. Hyperventilation invariably reduced cerebral blood flow and high CO_2 increased it. Changes in arterio-venous differences for oxygen were in the same direction and of the same general magnitude as were to be expected from the changes in flow.

The electrokymograph application as a photo-electric plethysmograph. FRED G. GILICK (by invitation), BERT R. BOONE (by invitation), GEORGE C. HENNY (by invitation) and MORTON J. OPPENHEIMER. *Depts. of Physiology and Medical Physics, Temple Univ. School of Medicine, Philadelphia, Penna.* To record heart border motion we have used the 931-A multiplier photo tube with its output connected directly to the string of the Cambridge Simpli-trol. It became evident that such a device could be used for recording other circulatory phenomena. We have had marked success with its application as a photo electric plethysmograph.

The 931-A multiplier photo-tube has an extremely high amplification factor and is remarkably stable. No amplifiers are needed between the photo-tube and the string galvanometer of the electrocardiographic record. Records are easily obtained with transillumination of finger or toe, or by a combination of reflected, scattered and transmitted light from any skin surface of the body. The record obtained has the same readability as any good electrocardiogram. At standard 25 mm/sec. speed the details of the plethysmographic record are clearly visualized. The string galvanometer electrocardiograph develops added usefulness in the field of the peripheral vascular diseases when fitted with this relatively simple accessory.

The renal clearance of thiosulfate in the dog. ALFRED GILMAN,¹ FREDERICK S. PHILIPS² (by invitation), and ERHOL S. KOELLE (by invitation). *Pharmacology Section, Medical Division, Chemical Warfare Service, Edgewood Arsenal, Md.* Thiosulfate can be determined in tungstic acid filtrates of plasma either by reacting the thiosulfate with iodate in the presence of HCl and thereby oxidizing to sulfate or by liberating iodine from iodate and oxidizing thiosulfate to tetrathionate. The former method is 8 times more sensitive than the latter and is highly accurate at plasma thiosulfate levels of 20 mg. per cent. Either method is directly applicable to urine suitably diluted.

Simultaneous determinations of the renal clearance of thiosulfate and creatinine in dogs (46 periods in 5 dogs) have revealed a clearance ratio of unity.

Only 70 to 80 per cent of intravenously injected thiosulfate was recovered in the urine. The loss for the most part occurred during and immediately following injection. After equilibration was com-

¹ Major, Sn-C, A. U. S.

² 1st Lt., Sn C, A. U. S.

mined by recorded responses to visual and auditory signals and by changes in ear opacity (blood content of the ear). The gram ranged from magnitudes which caused no visual symptoms, to those causing blackout. Anoxia was induced by breathing a gas mixture containing 11.5% oxygen and 88.5% nitrogen until a steady state was reached of Millikan oximeter readings (ca. 15 minutes), and maintained during the centrifuge tests. All subjects were at low oxygen tensions for 30-40 minutes. Return to normal was effected by breathing room air again for ca. 15 minutes.

Although oxyhemoglobin saturation was reduced to an average of 64% (range 59-75%), as determined by oximetry and Van Slykes, there was no significant decrease in gram tolerance (average 0.1 gram, maximum for blackout in any one case, 0.4 gram).

The results support and extend those reported by Gauer (*Luftfahrtmed* 9:104, 1944) [*The work described in this abstract was done under a contract with the Office of Scientific Research and Development*].

Further observations on the toxic factor in ischemic compression shock. HAROLD D. GREEN, J. MAXWELL LITTLE, and J. E. HAWKINS, JR. *Dept. of Physiology and Pharmacology, The Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C.* As a result of cross-transfusing dogs dying of ischemic compression shock with normal test and with ureter-ligated test dogs, it was concluded that a toxic factor is present in the blood of the traumatized dogs which can contribute to the death of test dogs only in the presence of renal failure (*Fed. Proc.* 4:26, 1945).

To test further the protective excretory capacity of the kidney we collected urine from the test and the traumatized dog at 15 min. intervals and infused it intravenously into a urine recipient dog whose own urine was also reinfused at 15 min. intervals (Little, Hawkins and Green, *Fed. Proc.* 1946). All urine was passed through a Seitz filter. The weight ratios of the traumatized and test animals to the recipient dog were 2.6 and 1.5 respectively.

One of 4 dogs infused with urine from traumatized and test animals died in 25 hrs., 3 of 4 control dogs infused with urine from cross-transfused normal dogs died in 20 to 61 hrs., and 6 of 14 control dogs infused from dogs auto-transfused between the femoral vessels died in 12 to 35 hrs. All others survived indefinitely. An average of 11.6 ml./kg. of donor urine was infused in the shock experiments and 23.6 and 10.3 ml./kg. in the control experiments. The mean arterial pressure remained at normal levels throughout the 3-7 hr. periods of infusion.

These experiments fail to demonstrate the presence of a significant toxic factor in the urine of test dogs cross-transfused with dogs dying of ischemic compression shock.

Effect of additional carbohydrate intake without altered insulin dosage upon oxidation of dextrose by subjects with controlled diabetes mellitus. JAMES A. GREENE, *Dept. of Medicine, Baylor Univ. College of Medicine, Houston, Texas*. The manner by which subjects with controlled Diabetes Mellitus utilize additional carbohydrate without extra insulin has caused a great deal of controversy. Three diabetic and two normal subjects were, therefore, studied in an open circuit metabolism chamber for the 24 hours of the fifth day of an average diabetic diet and again for the 24 hours of the fifth day of additional carbohydrate intake. The gaseous metabolism and nitrogen excretion were ascertained for each period and the oxidation of carbohydrate and fat were calculated from the non-protein respiratory quotient. Unmodified insulin was used and the first diabetic subject received 70 units, the second 55 units and the third 40 units daily throughout the study. The diet of each subject contained 1 gram of protein and 30 calories per kilogram of body weight per day. The caloric content of the diet increased by the amount of the added carbohydrate.

The oxidation of dextrose by the first diabetic subject rose from 200 to 290 grams when the carbohydrate intake was increased from 150 to 300 grams. In the second diabetic subject it increased from 175 to 260 grams when the intake was augmented from 125 to 325 grams, and it increased from 175 to 275 grams by the third diabetic subject when the intake rose from 125 to 260 grams of carbohydrate daily.

The oxidation of dextrose by the first normal subject increased from 125 to 400 grams when the carbohydrate intake was altered from 110 to 405 grams and by the second normal subject from 135 to 275 grams with an increase of intake of from 110 to 260 grams daily.

The oxidation of dextrose per hour rose in each instance with the additional carbohydrate intake without a corresponding increase in calories produced per hour.

DC potentials and ulnar nerve dysfunction. R. G. GRENELL and H. S. BURR (by invitation). *Section of Neuro-Anatomy, Yale Univ. School of Medicine*. By means of the DC microvoltmeter described in 1936 by Burr, Lane and Nims, measurements have been made of differences in potential between an indifferent electrode and a moving electrode placed on the skin surface in an area supplied by the nerve whose activity is under question. Readings were taken before and after blocking of the ulnar nerve with procaine or procaine-suprarenin, in normal human cases, in human cases with complete paralysis of the nerve or in various stages of regeneration, and in cases of sympathectomy of the extremity.

It has been found that following procaine block of a normal nerve, the surface potential difference

is shifted markedly positive—many cases showing almost complete reversal in polarity. If the nerve is severed or completely degenerated no shift is seen, and positive peaking of the potential during block is concomitant with regeneration—the shift increasing as regeneration progresses. The observation that these shifts occur even following sympathectomy leads to the suggestion that the E M F being measured is associated with a direct nerve-tissue relationship without any intervening vascular or sweating mechanism being necessary.

The data thus obtained show that surface potential differences are correlated with the functional status of peripheral nerves and that this method can be used clinically as a simple, quantitative test of peripheral nerve function. Experiments are in progress to examine the physiological mechanisms involved [Part of the work was carried out at the U S Naval Hospital at St Albans, Long Island].

Studies of the central or reflex control of the circulation several years after sympathectomy. KERTH S GRIMSON. *From the Dept of Surgery of Duke Univ School of Medicine and of the Univ of Chicago*. The effect of obstruction of the carotid arteries, stimulation of the sciatic nerves, inhalation of gas mixtures with deficient and with excess oxygen or with excess carbon dioxide, cervical vagotomy and central vagus stimulation, activation of the carotid sinus reflex and the vasomotor response of blood pressure and of volume of the spleen and of circulation through the leg, and the effect of adrenalin, atropine, and nicotine has been studied on normal dogs, and on dogs sympathectomized a few months and also dogs sympathectomized several years. The responses indicate that vasomotor control is largely abolished by complete sympathectomy but that after several years a definite but incomplete recovery occurs.

Centrifugal course of functional deterioration in motor nerve deprived of circulating blood. R A GROAT and H KOENIG (by invitation). *Inst of Neurology, Northwestern Univ Medical School, Chicago*. The medial popliteal trunk and contributing ventral roots were exposed in chloralose-anesthetized cats. Electrical thresholds of points on this circulated nerve preparation (nerve-roots + trunk) were determined as the least electrical stimulus evoking either a contraction of gastrocnemius or the "A" wave led from the distal end. Then the trachea was clamped and thresholds recorded until responses failed.

The most proximal point was invariably first to undergo increase in threshold, progressing to inexcitability. With time, successively more distal points underwent similar change.

The gradient of deterioration in the proximal 25–40% of the nerve differed from that in the distal 60–75%. At a given point in the proximal segment the time interval between first rise in threshold and inexcitability was short. Two or 3 cm distal to

a nearly completely inexcitable point there was little or no threshold change. In the distal segment rate of threshold elevation usually lagged at first, and points of moderately elevated threshold occurred along 5–6 cm of nerve. Then widely separated points became inexcitable within a short time.

Points 6 and 85% of the distance between proximal and distal ends of the nerve underwent 5-fold threshold increase in 13 and 96 minutes respectively.

Roots were completely inexcitable before onset of threshold elevation at mid-level of the nerve.

Slower motor fibers in roots deteriorated before faster ones, and in the trunk the fastest fibers survived longest [Aided by grant, National Foundation for Infantile Paralysis].

Changes in the acid-base balance of the blood during asphyxia. F S GRODINS, ALLEN LEIN (by invitation), and HARRY F ADLER. *Dept of Physiology, AAF School of Aviation Medicine, Randolph Field, Texas*. Changes in blood acid-base balance of lightly nembuthalized dogs asphyxiated either by tracheal obstruction or by pure nitrogen were studied. Total CO_2 content and pH of plasma from arterial or cerebral venous blood were determined, pCO_2 and bicarbonate content were calculated by means of the Henderson-Hasselbach equation.

In six obstructed dogs, mean arterial pH fell steadily from 7.40 to 7.19 after 6.5 minutes. At this time, blood pressure had fallen to zero. Arterial plasma bicarbonate content rose from 46.5 vol % to an average maximum of 58.0 three minutes after obstruction and then decreased to 52.7 vol % after 6.5 minutes. Arterial pCO_2 rose from 35.2 mm Hg to a maximum of 64.7 in 5.5 minutes and then fell slightly. In cerebral venous blood (3 dogs), an average maximum pCO_2 of 71.9 mm Hg was found. These changes indicate an early respiratory acidosis with a late metabolic acidosis superimposed.

In six animals asphyxiated with nitrogen, arterial pH rose to an average maximum of 7.72 at the height of hyperventilation. The corresponding pCO_2 value was 16.8 mm Hg. With respiratory depression and apnea, pH fell and pCO_2 rose. After 5.5 minutes, the pH had fallen to 7.37 which was below the control value of 7.43. The corresponding pCO_2 value was 39.8 mm Hg which was higher than the control value of 36.1. The original respiratory alkalosis appears to have been overcome by the late respiratory and metabolic acidosis so that both (H^+) and pCO_2 are above the control values at the time circulation fails.

Prevention of ulcer in Mann-Williamson dogs by the oral administration of intestinal extracts. M I GROSSMAN (by invitation) and A C IYR. *Dept of Physiology, Northwestern Univ Medical School, Chicago*. When Mann-Williamson dogs are

treated parenterally with upper intestinal extracts concentrated in regard to enterogastrone content, only 25 per cent of the animals develop ulcer as compared with 98 per cent of untreated controls (Ivy, Gastroenterology, 3 6, 1944) There is some question as to whether the beneficial effect of these extracts is due to their enterogastrone content because (1) the dose used causes only a slight and transient depression of acid secretion and (2) the protection afforded by this treatment persists after the injections have been stopped (in contrast with treatment by aluminum phosphate)

Variously prepared acid extracts of the upper intestinal mucosa of hogs have now been administered to Mann-Williamson dogs daily *by mouth*. Of 17 dogs so treated and observed from 3 to 17 months, 3 have developed ulcers in an average period of 6 months, 3 have died of other causes without ulcer in an average of 10 months, and 11 animals are living from 3 to 16 months post-operatively. In 3 of these 11 animals treatment was discontinued at the end of 9 months and from 5 to 7 months have now elapsed since cessation of treatment.

These results indicate that the oral administration of intestinal extracts is as effective as treatment by the parenteral route in preventing experimental post-operative ulcer. Inasmuch as enterogastrone concentrates do not depress gastric secretion when administered orally, further support is added to the concept that the enterogastrone is not the anti-ulcer factor in intestinal extracts. Furthermore, a product which can be produced in quantity and tested clinically in patients with peptic ulcer is afforded.

The origin of electrical activity from spinal afferent stimulation of the inferior olive of cats. HARRY GRUNDFEST *Dept of Neurology, College of Physicians and Surgeons, Columbia Univ, New York*. Electrical activity of the inferior olive of cats following spinal afferent stimulation has been recorded using needle micro-electrodes. The largest and earliest response occurs from contralateral afferent stimulation. It represents summated activity lasting about 20 msec. A smaller response, later by 1 to 2 msec, arises from ipsilateral stimulation, usually taking the form of 2 or more small, discrete spikes discharged at intervals 1 to 2 msec apart.

In a typical experiment, tibial or peroneal stimulation caused a contralateral olivary response after 5.9 msec. The afferent activity, carried in the ipsilateral dorsal column, arrived at the nucleus gracilis at 5.8 msec. The olivary response therefore cannot have arisen from activity initiated through the nucleus gracilis and must have been caused by impulses arriving in a more rapidly conducting tract. The only tract delivering impulses at the medulla earlier is the dorsal spinocerebellar. In

the above experiment, this tract delivered its impulses to the medulla in 4.4 msec, 1.5 msec prior to the onset of contralateral olivary activity. A variety of transection and stimulation experiments indicate that the earliest and largest activity of the inferior olive is initiated through impulses ascending in dorsal spinocerebellar fibers or in a parallel, contiguous, large fibered system. The interval of 1.5 msec between the arrival of impulses via Flechsig's tract and onset of contralateral olivary activity affords ample time for conduction of activity across the medulla and for relay into the olive.

Relationship of "psychoneurotic" changes to carbohydrate utilization in men on experimentally varied intake of B-complex vitamins. HAROLD GURTZKOW (by invitation), AUSTIN HENSCHEL and JOSEF BROZIK (by invitation) *Univ of Minnesota, Minneapolis*. Ten subjects were maintained, with constant activity, on diets restricted in thiamine, eventually resulting in acute deficiency.

The difference between fasting and post-ingestion blood sugar concentrations was determined 30, 60, and 90 minutes after ingesting 100 grams glucose, the sum of the three differences was used as an index of glucose tolerance. The average score on three scales of the Minnesota Multiphasic Personality Inventory—hypochondriasis, depression, hysteria—were used as a "psychoneurotic" index.

Both indices showed marked changes. For instance, four men who received the least thiamine had an average rise in their glucose tolerance index from 60 (control) to 118 mg % at the end of the acute deficiency, the corresponding psychoneurotic indices were 52 and 84 (normal average = 50, ± 10). However, the product-moment correlation between the two indices within individuals was only +.41 (39 pairs). In a similar experiment with 8 men maintained on varied intakes of the B-complex, again resulting in acute deficiency, with thiamine lack as the predominant factor, the correlation was +.28 (23 pairs). When the data for both experiments were pooled, the correlation was +.41 (62 pairs).

Hence in men on an inadequate intake of the B vitamins, particularly thiamine, there was a low but statistically significant correlation between the decreased ability, as measured by glucose tolerance, to utilize carbohydrates, and the tendency toward psychoneurosis. There is no evidence that this relationship is one of cause and effect rather than merely one of similar response to a third factor or factors. [This work was supported in part under a contract with the Office of Scientific Research and Development. Support from other sources will be acknowledged in final publication.]

Cerebral lactic acid and phosphates in concussion. (Read by title.) E. S. GURDJIAN (by invitation) and W. E. STONE *Wayne Univ College*

of Medicine and Grace Hospital, Detroit In 12 morphinized dogs, a trephine opening was made over each cerebral hemisphere The holes were threaded and one closed by a threaded plug Through the other the cerebral cavity was connected to a short column of saline in a long tube A weight was dropped on the column of liquid to produce concussion The tube and plug were removed and the brain frozen *in situ* Freezing began 15-67 seconds after injury Specimens of cerebrum were removed through the openings

Two animals were immobilized with dihydro-beta-erythroidine and maintained by artificial respiration In others, artificial respiration was given manually after concussion Arterial oxygen saturation remained adequate Concussion caused a sudden rise in blood pressure, and produced extensor spasm in animals not erythroidinized

No significant changes in phosphocreatine or adenosine triphosphate occurred Cerebral lactic acid was normal (as compared with previous data) in both hemispheres in 5 animals Slightly increased lactic acid was found subjacent to the column of liquid in 7 animals and contralaterally in two Since in 8 controls prepared in the same manner similar high values were found in 4 specimens from 3 animals, these changes may be artefacts due to the manipulations

From these results it appears that concussion can occur without significant changes in cerebral lactic acid, phosphocreatine or adenosine triphosphate observable 15 to 67 seconds after the blow A previous report showed similar results 15 to 85 minutes after injury The symptoms of concussion therefore are not referable to generalized anoxic changes in the brain

Cause and prevention of a type of leg deformity in brooder raised chicks C C GUTHRIE *Dept of Physiology and Pharmacology, School of Medicine, Univ of Pittsburgh* (Read by title) In an extensive study of numerous diets on growth¹ many of the chicks soon developed leg deformities, some to the extent of being incapable of walking or standing The floors were of smooth screen wire and it was obvious that the deformities were due to the slippery footing Ordinary rough wood plaster laths cut to proper length to fit into diagonal corners of the brooder compartments thus being held on edge on the floor, prevented further occurrence and alleviated the condition when not too far advanced Later when transferred to larger similarly floored battery compartments, some of the chickens soon showed symptoms of the same trouble which likewise was corrected by introducing rough sur-

the condition consisting mainly of strained adductor muscles and ligaments, slipped tendons, and partially dislocated and deformed joints There was no relation of the condition to the character of the feeds

Observation on work capacity, work performance, and certain metabolic processes when strenuous exercise was taken after isocaloric meals of low and high carbohydrate content JOHN HALDI and WINFREY WYNN (by invitation) *Dept of Physiology, Emory Univ, Emory Univ, Ga* On the basis of clinical observations it is stated in the literature that a high carbohydrate meal is conducive to a lowering of the blood sugar concentration several hours later and a concomitant reduction in work capacity Our experiments conducted on four subjects failed to confirm this assumption The experimental procedure was as follows On alternate days of the experiment the subjects ate isocaloric midday meals of a high and low carbohydrate content, respectively Approximately three hours later they rode on a bicycle ergometer to exhaustion, rested in the recumbent position for 10 minutes, and then rode to exhaustion

Throughout the experiment which included two 10 minute preliminary rest periods, two exercise periods with a 10 minute rest period intervening, and three 10 minute recovery periods, the expired air was measured and samples analyzed for determining oxygen consumption and carbon dioxide elimination Blood samples were taken at regular intervals for analyses of the sugar and lactic acid content

There was no significant difference in the amount of work done in the first exercise period or in the percentage recovery in the second exercise period after the two types of meals The blood sugar level immediately before exercise was higher after the meal rich in carbohydrate, but at the conclusion of the exercise periods and at the end of the recovery periods it was at approximately the same level as when a low carbohydrate meal was eaten Data will be presented on the respiratory exchange, muscular efficiency and lactic acid changes in the blood

Respiratory efficiency at altitude F G HALL *Dept of Physiology and Pharmacology, Duke Univ School of Medicine, Durham, N C and Aero Medical Lab, Wright Field, Dayton, Ohio* Results of analyses of arterial blood withdrawn from individuals at various low pressures indicate that an effective equilibrium between arterial blood and alveolar air is maintained at equivalent

factor in supplying available oxygen at rest or even in moderate exercise

The thermal (copper) man—a new instrument for the study of radiation and convection heat loss in man JOHN F HAIL, JR, (introduced by A P Gagge) *Aero Medical Lab, Air Technical Service Command, Wright Field, Dayton, Ohio* An electrically heated copper man, constructed by the General Electric Company, has been used to study the radiation and convection heat loss from both nude and clothed man Its total surface area is 1.71 square meters and is finished in dull black in order to closely simulate the radiation characteristics of a black body Operated on 110 volt AC current the control assembly consists of 13 separate units corresponding to various body and extremity areas The heating of specific regions is consequently under independent control while a master control regulates heat input to the body as a whole

Surface temperatures are measured with 32 copper-constantan thermocouples imbedded in the surface which are automatically or manually recorded depending upon the precision of measurement required Determination of copper man surface and clothing surface temperatures, after equilibrium with various heat inputs, affords precise measurement of the thermal insulation of various types of clothing assemblies

The thermal man permits the division of cold tolerance in man into two basic components (a) the thermal insulation afforded by the clothing itself, and (b) the biophysical response to the calorie demand of the environment Studies of the former type have now been largely completed and attention is being directed toward biophysical studies, based on this application of the method of the physical model These studies include regional analysis of heat loss from the body, determination of radiation and convection coefficients for the body and other biophysical characteristics

Radar measurement of rates of free fall of anthropomorphic dummies and man GEORGE HALLENBECK (by invitation), JACK GLAZIER (by invitation) and GEORGE MAISON *Aero Medical Lab, ATSC, Wright Field* (Read by title) Problems of parachute escape and present knowledge of high shock forces resulting from parachute opening at high altitudes demand more information on man's rate of free fall for prediction of wind velocities he must withstand and duration of exposure to cold and anoxia Figures thus far available are based almost entirely on theoretical considerations To actually measure rates of free fall, anthropomorphic dummies and a man were tracked by radar during free fall from altitudes up to 40,000 feet Analysis of radar data provided vertical velocities at various altitudes and curves of altitude versus time during descent A freely falling body reaches terminal velocity when its

drag equals its weight At terminal velocity, drag = weight = $C_D S = \frac{\rho v^2}{2}$ where C_D = drag coefficient, S = drag area, ρ = air density, and v = velocity The $C_D S$ of a nonsymmetrical object varies with changes of attitude during fall With weight and velocity known and with air density obtained from standard atmosphere tables, $C_D S$ values for the dummies and the man were calculated thus

	Dummy weight, lbs			Man, lbs
	180	220	280	240
Number of Drops	8	6	2	1
Mean $C_D S$	5.53	6.30	5.99	3.97
Standard Deviation	0.37	0.35	0.29	0.26
No of Observations	75	60	87	24

More data on rates of free fall of man are needed to discover whether the fact that this man had a lower $C_D S$ and fell faster than the dummies is the exception or the rule By assuming $C_D S$ values in the range of 3.5 to 7 and various weights, one can draw predictive curves of time required to fall freely at terminal velocity from any given altitude to sea level and calculate wind velocities encountered during fall

Comparison of effects of positive G on subjects studied at both the Mayo and Air Technical Service Command Centrifuges G A HALLENBECK (by invitation), E H WOOD, E H LAMBERT and S C ALLEN *Acceleration Lab, Mayo Aero Medical Unit, Rochester, Minnesota, Aero Medical Lab, Engineering Division, AAF Air Technical Service Command, Wright Field, Ohio* G tolerances of twelve men were determined on the ATSC centrifuge (radius 20 feet) and on the Mayo centrifuge (radius 15 feet) At the Mayo laboratory, tests were run in an illuminated room, at ATSC, in darkness The time from 1.5 g to 5 g was 2.6 seconds on the Mayo centrifuge and 1.8 seconds on the ATSC centrifuge In both laboratories (a) duration of maximal g was 15 seconds, (b) environmental temperature was 70 to 72° F, (c) subjects were urged to relax, (d) vision was tested using similar light signal systems, (e) the g-time curves, response to light signals, electrocardiogram, heart rate, ear pulse and ear opacity were recorded Recording methods differed technically in some cases

Average accelerations at heart level at which vision was dimmed, lost peripherally and lost completely were 4.3 g, 4.8 g and 5.3 g, respectively, on the ATSC centrifuge These values were 0.6 g higher ($P < 0.001$) than those obtained on the Mayo centrifuge

Heart rates prior to g exposure averaged ten

beats per minute faster on the ATSC centrifuge, suggesting that the differences in g tolerance obtained are related more to differences in psychological factors associated with exposure to g on the two centrifuges than to any physical differences between the two machines

Comparison of the time concentration curves in arterial blood of dye injected at a constant rate with that of dye injected intravenously W F HAMILTON and JOHN W REMINGTON *Dept of Physiology, Univ of Georgia School of Medicine, Augusta, Georgia* When a foreign substance is injected into a vein at a constant rate, it is said to reach a uniform concentration in the arterial blood before recirculation. Such a plateau, if it exists, can be used to indicate the cardiac output. Published evidence for the plateau is elusive and contradictory. Theoretical considerations lead to questioning its existence.

A solution of brilliant vital red was injected at a constant rate into the jugular vein, and the concentration of dye in the arterial stream was sampled about every second. Curves so made showed a steady rise which continued for a few seconds longer than the injection. When the injection is made instantaneously, the time concentration curve is well known, both with and without recirculation (*Am J Physiol*, 89 302, 102 550). The curve resulting from a continuous injection should be predictable from an integration of a series of curves made by successive instantaneous injections. Three forms resulted from these calculations, each similar to those found experimentally. (1) With flow that does not recirculate, the concentration asymptotically approaches a level predicting the flow. This level is not closely approximated until after the lapse of at least four times the period needed for the first dye to appear. With recirculating flow, the curve may either (2) continuously rise, or (3) if injection ceases after 10 to 25 sec, reach a rounded summit whose height varies with the injection time. The concentration at this summit includes twice circulated dye and cannot be used to calculate the cardiac output.

Somatotopic localization in the cerebellum JOHN L HAMPTON (by invitation), CLINTON R HARRISON (by invitation) and CLINTON N WOOLSEY *Dept of Physiology, Johns Hopkins Univ, School of Medicine, Baltimore 5, Md* In a previous communication (*Fed Proc*, 1945) we described localized motor and inhibitory effects produced by electrical stimulation of anterior lobe and lobulus simplex in cat and dog. Study has now been extended to monkey and stimulations of most of cerebellar surface of cat and dog have been made.

Respecting *anterior lobe* and *simplex* we may add (1) Strongest effects in tail are obtained from lingula (cat). (2) In monkey, as compared with cat

and dog, the lateral anterior lobe, yielding initial ipsilateral active extension, is relatively more developed than the medial, which gives ipsilateral active flexion and extensor inhibition. This suggests an explanation of known differences in effects of cerebellar ablation on muscle tonus in lower and higher forms. (3) Simplex, in addition to controlling neck and eyes, produces opening and closure of jaws, contraction and relaxation of orbicularis oculi, orbicularis oris and nasolabialis (cat and dog).

From *paramedian lobules* (cat, dog, monkey) active flexions and extensions, usually ipsilateral, sometimes bilateral, were produced. Inhibition was not prominent. Somatotopic localization is as follows: upper folia, face, middle folia, arm, lower folia, leg and tail.

Other results were as follows: *pyramis*, bilateral movements of arm and leg, *tuber vermis*, conjugate eye movements, *crus I and II*, no definite effects.

Somatotopic localization is similar to that described for afferent systems (Snider and Stowell, Adrian, Dow and Anderson). A parallelism between anterior lobe simplex and Rolandic cortex and between paramedian lobules and cortical somatic area II (Woolsey, *Fed Proc*, 1946) is indicated.

Depolarisation in the spinal cord caused by asphyxiation A VAN HARREVELD *California Inst of Technology, Pasadena* During asphyxiation of the spinal cord, the gray matter becomes negative with respect to the outside of the cord. The manner of asphyxiation determines the development of this potential difference. When the respiration is simply stopped it takes 45 to 60 seconds before the first indication of the negativity of the gray matter becomes apparent. When the oxygen is washed out of the system by making the animal breathe nitrogen, the potential difference starts to develop after 20 to 30 seconds. Finally when asphyxiation is caused by clamping the aorta between the diaphragm and the coeliac artery the first indication of negativity of the gray matter is seen after about 10 seconds. Potential differences up to 10 millivolts have been recorded. When after an asphyxiation of 1 to 2 minutes the cord is again oxygenated, the potential difference disappears usually within one minute. It is likely that this negativity of the gray matter is the expression of the depolarisation of the parts of the neurons most sensitive to oxygen lack. According to the membrane theory this would create a potential difference between the depolarised and the intact parts of the neuron.

Ventricular fibrillation and standstill in coronary occlusion, anoxia and hemorrhage A SIDNEY HARRIS *Dept of Physiology, Western Reserve Univ Medical School, Cleveland, Ohio* During recent years numerous observations upon the

experimental conditions simulating natural causes of death have accumulated. Among these experimental conditions are (1) occlusion of a coronary artery, (2) generalized anoxia produced by breathing air with a progressively lowered oxygen content, and (3) hemorrhage.

Upon clamping the anterior descending artery the ventricles fibrillated within less than ten minutes in twenty-five out of forty-six trials in nine out of fourteen animals. Of the twenty-one failures to fibrillate during occlusion four fibrillated soon after release of the clamp.

In forty-two dogs subjected to generalized anoxia there was one fibrillation death and all others ended in ventricular standstill. In some cases the auricles continued beating for some time after the ventricles ceased their action.

In fourteen dogs dying from hemorrhage there were two fibrillations and twelve cases of pacemaker failure usually followed by a brief period of nodal rhythm.

Frequent fibrillations in coronary occlusion affecting a local area and rarity of fibrillation in conditions affecting all parts is consistent with our previous findings that (1) fibrillations are prone to occur under conditions which produce rapidly discharging ectopic foci, (2) the ischemic-nonischemic boundary in coronary occlusion is a source of ectopic impulses and (3) ischemic areas are hypoactive and not likely to initiate impulses.

The influence of extrinsic gastro-intestinal innervation on dexedrine induced anorexia.

C HARRIS (by invitation) and A C IVEY, *Dept of Physiology, Northwestern Univ Medical School, Chicago*. A satisfactory procedure for the study of dextro-amphetamine (Dexedrine) induced anorexia in dogs has been developed. Each day, at the same hour, a weighed dish of food is presented to each animal. After 45 minutes the dish is removed and again weighed. Every meal was the same in composition and water content.

The experimental design consisted of (1) establishing the range of daily variation of food intake and body weight, (2) the modification of food intake and body weight induced by (a) the medication, (b) supradiaphragmatic bilateral vagotomy, (c) bilateral splanchnicectomy and (d) medication after the surgical procedures.

The results observed were (1) Daily food ingestion and body weight were found to be quite stable during control periods. (2) Administration of Dexedrine, subcutaneously, one hour before feeding caused anorexia proportional to the dose, the animals ate ravenously the first day after the cessation of the period of medication. This occurred on every one of 21 such occasions. (3) Neither vagotomy, splanchnicectomy nor the combination of the two surgical procedures modified the daily

studied. (4) The modification of food intake and body weight caused by Dexedrine was the same after vagotomy and splanchnicectomy (either alone or together) as before surgery.

It is concluded from these observations that Dexedrine induces anorexia by acting on the central nervous system. [*This work was aided in part by a grant from the Smith, Kline and French Labs.*]

A sodium retaining substance of the adrenal. FRANK A HARTMAN and JONATHAN S THATCHER (by invitation) *Dept of Physiology, The Ohio State Univ, Columbus*. A substance highly potent in its ability to cause retention of sodium in the body has been prepared in three ways, viz by fractional solvent precipitation, by molecular distillation, and by chromatographic adsorption. The latter appears to produce little loss in potency, which is not true for the other methods. There is great difference in the behavior of this substance and desoxycorticosterone (DC) on a column of alumina. Their solubilities are also quite different. This substance is soluble in methyl and ethyl alcohol, propylene glycol, glacial acetic acid, and acetic anhydride, partially soluble in acetone, and insoluble in chloroform, ethylene dichloride, benzol, carbon tetrachloride, petroleum and ethyl ethers and pyridine. It is somewhat soluble in water and insoluble in dilute (0.1 N) hydrochloric acid, but very soluble in dilute (0.1 N) sodium hydroxide. It distills above 120°C at 10⁻³ mm Hg, while DC distills at 90-95°C at 10⁻³ mm Hg. It has no effect on potassium excretion. Treatment with 0.1 N HCl destroys a considerable proportion of the potency and forms NaCl. Acetylation destroys part of the potency with evolution of a large amount of heat.

Injury of the inner ear produced by exposure to loud tones. J E HAWKINS, JR,¹ H DAVIS and M H LURIE (by invitation) *Depts of Physiology and of Otolaryngology and Laryngology, Harvard Medical School, Boston*. Severe damage to the cochlea of guinea pigs was produced, without injury to eardrum, ossicles or vestibular apparatus, by exposure to loud (140 to 157 db) pure tones. The least damage, (loss of mesothelial cells from the lower surface of the basilar membrane) was produced by 1000 cycles at 140 db for 3 minutes. More intense tones and longer exposures caused degenerative changes in the sensory cells, rupture and dislocation of the organ of Corti, and ultimate degeneration of nerve fibers and ganglion cells. Mild damage was localized, nearer to oval window for high, nearer to helicotrema for low tones, but severe exposure caused widespread permanent damage. The aural microphonics were impaired by severe exposure. There was some general corres-

¹ Present address: Department of Physiology, Bowman Gray School of Medicine.

pondence, both as to frequency (place) and degree, with anatomical changes, but their relationship to anatomical damage and to hearing losses determined by conditioned reflexes is too erratic to make the "electrical audiogram" a reliable method of assessing injury to the ear

Hypotensive reactions to cross-transfusion in dogs J E HAWKINS, JR, HAROLD D GREEN, and J MAXWELL LITTLE *Dept of Physiology and Pharmacology, The Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N C* (Read by title) In 15 of 33 cross-transfusion experiments between pairs of dogs anesthetized with morphine-pentobarbital, a sharp decline in the mean arterial pressure of one or both animals occurred within 5-15 min and with the exchange of as little as 200 ml of blood In 13 of the 21 animals showing the reaction, the pressure dropped to 50 mm Hg or less, and the cross transfusion was temporarily stopped The period of hypotension lasted 5-80 min (average 20 min) In only two animals did a second reaction occur when the cross transfusion was resumed

The reaction was not accompanied by any change in the rectal temperature of the animal, nor did the color of the urine indicate that hemolysis had occurred

The plasma of all 21 dogs showing hypotensive reactions had been matched against the cells of the opposite member of the pair by the Landsteiner technique In no instance was agglutination seen In 2 matches slight agglutination was seen but in these animals no reaction occurred Moderate rouleaux formation was observed in the plasma of 6 dogs and each of these developed moderate to marked reactions In 12 experiments in which reactions occurred, no evidence of incompatibility was observed when the bloods were cross-matched

The 17-ketosteroids in plasma, urine and sweat OSCAR HECHTER (by invitation) and GREGORY PINCUS *The Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts* To obtain information concerning the blood concentration and the chemical state of circulating 17-ketosteroids, comparative studies on the 17-ketosteroids in human plasma, urine, and sweat were undertaken While the absorption curves obtained with ketonic neutral urinary extracts using either the *m* dinitrobenzene or the SbCl_5 reaction closely resemble those of pure 17-ketosteroids, similar extracts of both plasma and sweat exhibit atypical absorption curves exhibiting no characteristic ketosteroid peak Study of the chromogenic material in plasma revealed that approximately 10% is directly extractable with ether, that the major fraction (ca 65%) is ether extractable after alcohol-ether heat denaturation of the plasma proteins, that acid hydrolysis of the material in the alcohol ether filtrate yields an additional 15%

and that there is approximately 10% remaining with the denatured plasma protein Purification of the ketonic material of the plasma fractions to remove extraneous chromogens suggests that certain fractions may contain true 17-ketosteroid To explain the differences observed between the chromogens in urine and those in plasma and sweat, it is necessary to postulate renal reabsorption of the atypical plasma chromogens Preliminary studies indicate that this renal reabsorption mechanism may be affected by heat stress

Heat death, heat injury and toxic factor L V HEILBRUNN *Dept of Zoology, Univ of Pennsylvania* A study was made of the heat death of rats and guinea-pigs and the survival time at various temperatures was noted When the legs of rats are exposed to temperatures of 45°C , the animals die in about 2½ hours Guinea-pigs are not so sensitive to partial exposure Death is believed to be due to the production of toxic factor by heat-killed tissues, especially muscles Watery extracts of muscles injected intraperitoneally into rats cause death with symptoms very similar to those observed when animals die in the hot room In heat-killed rabbits and scalded dogs, it was sometimes possible to show presence of a high concentration of toxic factor in blood The toxic factor contains potassium but is not solely potassium This is shown by the blood experiments but even more clearly by experiments in which protoplasm of sea-urchin eggs is used as an indicator for toxic factor The surface precipitation reaction of oxalated sea-urchin eggs occurs only if thrombin-like substances are present Such substances can readily be demonstrated in muscle extracts Attempts to concentrate toxic factor in muscle extracts often lead to loss of toxic factor Apparently toxic factor may combine with an insoluble (protein) phase and be lost from solution Also the presence of sodium seems to favor the loss in potency of toxic factor These results are to be correlated with the fact that injection of thrombin produces shock (Tagnon), also with the fact that NaCl is a therapeutic agent both for burns and for heat prostration

Gonad-pituitary relationship—metabolism of pituitary gonadotrophins by ovaries transplanted into the spleen CARL G HELLER, (by invitation), EDWIN C JUNGCK, (by invitation) *Dept of Physiology and Medicine, Univ of Oregon Medical School, Portland*, WARREN O NELSON, *Dept of Anatomy, Univ of Iowa, Iowa City*, and HELEN A WINTER (by invitation) *Dept of Anatomy, Columbia Univ, New York* Regulation of gonadotrophic storage, secretion and excretion and of ovarian secretion may theoretically be governed by (1) action of estrogens upon the pituitary gland, (2) action of estrogens upon the ovaries and (3)

metabolizing of circulating gonadotrophins by ovarian action

In order to test whether the ovary "uses" or metabolizes gonadotrophins, ovaries of adult albino rats were auto-transplanted into the spleen, thus materially reducing the amount of estrogen reaching the general circulation and thereby the pituitary

Estrogen was inactivated by the liver to such an extent that in effect the rats became castrates as judged by atrophy of vaginal cells, atrophy of the uterus, and hypertrophy of the thymus

The ovaries transplanted to the spleens increased in weight from 2 to 5 times in 30 to 90 days

Assays of the anterior pituitaries of the experimental group were compared with assays of normal, castrated and ovaries-transplanted-to-spleen-with-vascular-adhesions-to-systemic-circulation control groups. The experimental group did not exhibit a rise in gonadotrophins that the castrated controls did

It is concluded that ovaries metabolize gonadotrophins, that ovarian growth activity is partly regulated by blood estrogen level and that the liver is capable of inactivating estrogens secreted by viable ovaries transplanted to the spleen

Response of blood pressure and pulse rate of the new born rat to changes in body temperature
H F HELMHOLZ, JR (introduced by F C Mann)
Division of Experimental Medicine, Mayo Foundation, Rochester, Minnesota Since it has been shown that the new born rat is essentially a poikilothermic animal, the blood pressure and pulse rate of a series of these animals was studied in response to temperature changes. The carotid arteries were cannulated and the mean blood pressure and the pulse rate recorded using a damped glass spoon manometer. Rectal temperatures were recorded simultaneously by means of a differential thermocouple. The temperature of the animals was influenced by means of water flowing through the metal platform on which the animals were held.

From the starting blood pressure and pulse rates at 37°C, lowering of the body temperature caused parallel fall of both pulse rate and blood pressure. Reheating from as low as 20°C brought values to essentially original levels. Raising the body temperature above 37°C caused at first parallel rise in blood pressure and pulse rate. Increase beyond a certain temperature, quite variable in this series, caused a drop in blood pressure but still further increase in pulse rate. Cooling to 37°C from temperatures as high as 43°C brought values again to essentially original levels after exposures up to one half hour duration.

The electrokymograph, an apparatus for recording motion (for example, that of the heart shadow border) GEORGE C HENNY, BERT R BOONE and W EDWARD CHAMBERLAIN (introduced by Morton

J Oppenheimer) *Depts of Radiology and Medical Physics, Temple Univ School of Medicine, Philadelphia, Penna* The 931-A multiplier photo-tube, used with a recording galvanometer, will accurately record variations in light intensity at the photosensitive surface of the tube. Such variations in light intensity may be produced in various ways from physiological motions in the human or animal body. With proper application these motions are recorded with fidelity, (Amer J Roentgenol 54 217-229, 1915). For example the motion of a selected point on the border of the fluoroscopic silhouette of a patient's heart may be recorded. This is done by placing a small piece of fluorescent screen directly over the light aperture of the photo-tube. The fluoroscopic x-ray beam, after passing the selected part of the heart border, traverses a series of apertures in a simple arrangement of lead diaphragms and falls upon the fluorescent screen. The motion of the heart border produces variations in the amount of light emitted by the screen. Resultant variations in the electrical output of the phototube are readily recorded by a string galvanometer on moving bromide paper.

Other applications, with and without the fluoroscope, readily suggest themselves. For example, very successful plethysmographic records have been obtained.

The effects of anoxia on the capillary permeability of the human arm J P HENRY, IRENE KLAIR, ELI MOVITT, and J P MEEHAN (introduced by P Greeley) *from the Dept of Aviation Medicine, Univ of Southern California, Los Angeles* The cuff technique of E M Landis, et al, J Clin Invest 11 717, 1932, was employed to study the effects of anoxia on capillary permeability. Preliminary experiments were made to determine whether consecutive applications of congestion would give consistent results. Four subjects were submitted at sea level to 30 minutes of venous congestion (60 mm Hg) twice repeated with a rest period of 60 minutes between experiments. Hematocrit, hemoglobin, and plasma protein estimations were made. The mean fluid loss found in six such double experiments was in the first experiment 5.8 ± 0.5 cc and in the second 6.3 ± 0.6 cc.

In a second series, one of the two consecutive experiments was run at some altitude between 18-20,000, i.e. with an oxyhemoglobin value of 60-70%. The mean estimated fluid loss for ten experiments at altitude was 5.0 cc ± 0.8 cc. The corresponding sea level value for this experimental series was 5.4 cc ± 0.8 cc. The calculated percentage of protein in the filtrate in the experiments at sea level was 0.10 ± 0.10 gms %. The corresponding figure for the altitude runs was 0.25 ± 0.06 gms %. However, there is no statistically significant difference between these figures. In addition, analysis

of the standard error of the fluid loss results shows that there is less than 1 chance in 100 that the loss at sea level differs by more than 20% from that at altitude [This work was done under a contract with the Office of Scientific Research and Development]

The deterioration of brief endurance work capacity during semi-starvation AUSTIN HENSCHEL *Laby of Physiological Hygiene, Univ of Minnesota, Minneapolis, Minnesota* The capacity to perform brief, severe physical work (run on motor-driven treadmill until exhausted or for 5 minutes at 8 6% grade and 7 miles per hour) was measured on 34 young men before and at 12 and 24 weeks of semi starvation (cf Keys, Fed Proc 1946) Average "fitness" scores, time of run in seconds and total kilogram-meters of work for the control period, and 12 and 24 weeks of semi-starvation were respectively 65 6, 33 1, 18 5, 245, 106, 52, 4813, 1693, 782 "Aerobic" work pulse rates (30 minutes 3 5 m/hr 10% grade) did not change The per cent deterioration during semi-starvation for "fitness" score, time of run and total kilogram-meters of work were 72, 79 and 84, respectively In starvation "fitness" scores which involve heart rates are misleading because obligatory bradycardia is associated with starvation debility In view of the small change in maximal oxygen transport per kilo of body weight and per kilo of active tissue (Taylor, Fed Proc 1946), the constant aerobic work pulse rates, and the large decrease in kilogram-meters of work performed, it is concluded that deterioration in brief endurance work capacity during semi starvation is primarily due to muscular weakness rather than to circulatory inadequacy The conclusion is further strengthened by the observation that the runs were terminated by leg muscle exhaustion without severe dyspnea or circulatory distress [This work was supported in part under a contract with the Office of Scientific Research and Development Support from other sources will be acknowledged in final publication]

The effect of semi-starvation on the emptying of the human stomach AUSTIN HENSCHEL and ANGIE MAE STURGEON (by invitation) *Laby of Physiological Hygiene, Univ of Minnesota, Minneapolis, Minnesota* (Read by title) Gastric emptying times were measured on 18 young men before and after 6 months of semi starvation during which time the average loss in body weight was 24 per cent The standard gastric meal used consisted of 40 grams of oatmeal cooked in 300 cc of lightly salted water and 60 grams of barium sulphate X-rays were taken at 5, 30, 60 and 90 minutes after the meal was eaten After 90 minutes the progress of the meal was followed at 15 minute intervals by fluoroscopy until the stomach was empty Between X rays and fluoroscopy, the subjects

remained seated The gastric shadows were traced from the X-ray films on paper and the areas measured with a planimeter The areas at 30, 60, and 90 minutes were expressed in percentage of the 5-minute area The emptying times before and after semi-starvation were 175 ± 32 and 226 ± 70 minutes respectively with a highly significant mean difference of 51 minutes Of the 18 subjects at the end of semi-starvation, 11 had prolonged emptying times, 6 had no change, and 1 had a shorter emptying time There was some decrease in gastric motility during the entire emptying phase but the greatest depression occurred after 90 minutes [This work was supported in part under a contract with the Office of Scientific Research and Development Support from other sources will be acknowledged in final publication]

The recovery of capacity for physical performance following experimental malaria in man AUSTIN HENSCHEL, HENRY LONGSTREET TAYLOR and ANCEL KEYS *Laby of Physiological Hygiene, Univ of Minnesota, Minneapolis, Minnesota* (read by title) Twelve normal young men who had been maintained in this Laboratory for 6 months under standardized dietary and activity conditions were inoculated with the McCoy strain of tertian malaria After a minimum of 193 degree-hours of temperature above 101°F the malaria was terminated by quinine sulphate Functions related to performance capacity were tested before and at regular intervals during 4 to 8 weeks after the experimental malaria The deterioration of functions during the febrile state as per cent of control values and the improvement of functions during the first 20 to 24 postfebrile days as per cent of the deterioration were hemoglobin 22 and 87, blood lactate 12 minutes after "anaerobic" work 79 and 74, blood pyruvate 12 minutes after "anaerobic" work 32 and 60, maximal oxygen transport 17 and 49, maximal ventilation 12 and 57, "anaerobic" respiratory efficiency 28 and 55, aerobic work pulse 21 and 96, aerobic recovery pulse 32 and 90, and postural adjustment scores 55 and 83 Harvard fatigue test scores were 83% of normal at 22 days There was no deterioration in aerobic oxygen consumption, ventilation and respiratory efficiency The aerobic work and recovery pulse rates returned to normal in 20-24 days Functions associated with maximal oxygen transport and with postural adjustment returned to normal in 6-8 weeks The relative rates of improvement of functions after malaria are similar to those observed in normal young men after 3 weeks of enforced bed rest [This work was supported in part under a contract with the Office of Scientific Research and Development Support from other sources will be acknowledged in final publication]

The quantitation of cutaneous vascular reactions with the photoelectric plethysmograph A B

HERTZMAN, W C RANDALL and K E JOCHIM from the Dept of Physiology, St Louis Univ School of Medicine, St Louis, Mo Changes in skin blood content as recorded by the photoelectric plethysmograph may be quantitatively expressed by comparison with the deflection produced by the insertion of a standard glass sheet between the photoelectric cell and the skin, this deflection is called the "filter unit" The volume equivalent of the "filter unit" on the finger is approximately 2.6×10^{-4} cc/cm² of skin The blood content and volume pulse of the skin usually vary together in such a manner that the change in the former is about 3-4 times greater than that in the volume pulse, deviations from this relationship (as in the finger's reactions to cold or in vasomotor reactions in forearm skin) imply changes in tone on the venous side, probably in the subpapillary venous plexus

Measurement of cutaneous blood flow The linear relation between the skin flow and the amplitude of the photoelectrically recorded cutaneous volume pulse has been established by calibration experiments on the finger The flow equivalent of the "filter unit" thus determined is approximately 0.10 cc/cm²/min Applications to the examination of regional differences in basal, resting and maximal cutaneous blood flows will be illustrated [Aided by the American Medical Association]

The effect of intravenous nitrogen on the respiration and circulation of the cat A W HETHERINGTON and R A MILLER (by invitation), Dept of Physiology, AAF School of Aviation Medicine, Randolph Field, Texas The effects of intravenous injection of nitrogen on respiration and circulation were studied in cats anesthetized with urethane Twenty-one cats received nitrogen at rates of 0.1-0.6 cc per minute for periods ranging from 17 minutes to 4½ hours

During the period of injection the most striking constant effects were tachypnea, bradycardia, and anoxemia and cyanosis Eleven animals showed no appreciable change in blood pressure In 10, blood pressure fell either slowly or abruptly Respiratory failure occurred in 7 animals, 6 of which were revived by artificial respiration after the injection of nitrogen was stopped

After the injection was discontinued 14 cats were sacrificed after periods up to 19 hours when recovery had apparently occurred In this group respiratory rate, pulse rate, and blood pressure returned to normal values, although some cyanosis frequently persisted At autopsy the lungs of the recovering animals showed some areas of atelectasis, and edema of the tissues about the pulmonary blood vessels

The remaining 6 cats died within 4-6 hours after the halting of nitrogen injection During the post-

and marked tachypnea persisted until a short while before death Blood pressure increased somewhat during the early post-embolic period, but then gradually declined to shock level Cyanosis and anoxemia continued to be evident No hemocentration was observed in 4 of these cats, autopsy revealed lung changes no greater than in many animals which recovered High hematocrits and severe lung damage occurred in the other two

Renal excretion of cinchona alkaloids and some quaternary base derivatives and their effect on renal hemodynamics EDWIN P HIATT and VIRGINIA SMIRIE (by invitation) Dept of Physiology, North Carolina School of Medicine, Chapel Hill, North Carolina The manner of excretion of quinine, quinidine, cinchonine and cinchonidine and two quaternary base derivatives (quinine methochloride and quinine ethochloride) is being studied, using dogs for experimental animals In addition, we are investigating the effect of the administration of these drugs on the renal blood flow, (measured by the clearance of p-aminohippurate), and on the glomerular filtration rate, (measured by the creatinine clearance)

Less than 25% of a given dose of any of these substances can be recovered in the urine All of them are excreted by glomerular filtration with some reabsorption in the renal tubules The rate of excretion of the alkaloids is particularly limited by the fact that a large fraction of their plasma concentration is bound to plasma proteins and hence not filtrable at the glomeruli The renal plasma clearance of the alkaloids is only 10 to 20% of the glomerular filtration rate at plasma concentrations of 4-8 mgm per liter The quaternary base derivatives are more rapidly excreted, their plasma clearances, at plasma concentrations above 10 mgm per liter, closely approaching the glomerular filtration rate

In most of our dogs the oral administration of quinine or quinidine causes an increase in renal blood flow and glomerular filtration without a marked alteration in mean blood pressure

The influence of diethylstilbestrol on the systolic blood pressure of normal rats HENRY C HILL, JR (Introduced by G S Eadie) Dept of Surgery, Duke Univ School of Medicine, Durham, North Carolina Grollman et al (J Pharmacol & Exp Therap 69:149, 1940) administered diethylstilbestrol orally and reported hypertension in normal rats Leatham and Drill (Amer J Physiol 139:17, 1943) likewise obtained hypertension after intramuscular injection of diethylstilbestrol On the other hand, Matthews et al (Endocrinology 25:177, 1943) employing the oral route reported no significant change of systolic blood pressure It became of interest to test again the effect of intra-

24 successive daily injections of 10 mgm of diethylstilbestrol in 0.2 cc of cottonseed oil the average blood pressure range was from 98 to 122 mm Hg. Periodic blood pressure determinations up to the 79th day revealed that the blood pressure remained within normal limits. Slight elevations of average blood pressure occurred after 7 or 8 injections lasting several days. However, hypertensive blood pressure levels were never attained.

These results confirm the findings of Matthews et al that diethylstilbestrol does not raise the systolic blood pressure to hypertensive levels in the normal rat.

Effect of pentothal anesthesia on canine cerebral cortex. HAROLD E. HIMWICH, EDMUND HOMBURGER (by invitation), BENJAMIN ETSTEN (by invitation), ROBERT MARESCA (by invitation), GEORGE YORK (by invitation), and WILLIAMINA A. HIMWICH (by invitation). *Dept. of Physiology and Pharmacology, Albany Medical College, Union Univ., Albany, New York.* A series of 7 dogs under pentothal anesthesia were prepared by trephination of the cranium over superior longitudinal sinus and exposure of the femoral artery. While an animal was respiring a mixture of 15% nitrous oxide, 21% oxygen and 64% nitrogen, samples of blood were collected simultaneously from the superior longitudinal sinus, draining the cerebral cortex and femoral artery. The blood was analyzed for oxygen and nitrous oxide in order to determine the cerebral metabolic rate according to the method of Kety and Schmidt. Determinations were made in two depths of anesthesia: one in which the anesthesia was the lightest possible and still permit manipulations and another in which nocuous stimuli evoked no apparent responses. The average cerebral metabolic rate for light anesthesia was 5.9 cc oxygen/100 gm tissue/minute and for deeper depression 2.5 cc oxygen/100 gm tissue/minute, a reduction of 56%. Similarly, the AVO₂ difference fell on the average 40% and cerebral blood flow 22%. The metabolic rate in light anesthesia is higher than that obtained by the same methods in monkey and in man, in whom, however, the venous blood did not come almost entirely from the cerebral cortex. If this fast metabolism in the dog is not caused by a species difference, it may be ascribed to the cortex uncontaminated by subcortical influences. [This study was aided by a grant from the Winthrop Chemical Company Research Fund.]

Brain metabolism in unanesthetized and anesthetized man. WILLIAMINA A. HIMWICH (by invitation), EDMUND HOMBURGER (by invitation),

observations were made. Blood was drawn simultaneously from the right and left internal jugular veins and the femoral artery to determine the right and left cerebral AVO₂ differences and the right and left cerebral blood flows, which were measured according to the method of Kety and Schmidt, in order to calculate cerebral metabolic rate. When results from both right and left sides are averaged, the oxygen consumption of the brain in the unanesthetized man is 3.3 cc oxygen/100 gm tissue/minute. This value, however, represents two groups: a higher one with 3.9 cc oxygen/100 gm tissue/minute and a lower one with 2.7 cc oxygen/100 gm tissue/minute. Because of the asymmetric venous return, the cortical component usually appears preponderantly in one of the two internal jugular veins, and it is concluded that the portion of the brain with the higher metabolic rate is the cortex.

In every instance, pentothal anesthesia induces a depression in metabolic rate. The average during anesthesia is 2.1 cc oxygen/100 gm tissue/minute, a reduction of 36% from the control value. The pattern of pentothal anesthesia shows that cortical oxidations are depressed earlier and more profoundly than those of the rest of the brain, which in turn may also be subjected to metabolic inhibition.

Organic phosphates and insulin. WILLIAMINA A. HIMWICH (by invitation) and HAROLD E. HIMWICH. *Dept. of Physiology and Pharmacology, Albany Medical College, Union Univ., Albany, New York.* Previous observations on the influence of insulin upon organic phosphate compounds were made on liver and muscle and were concerned chiefly with turnover rates. The present investigation included not only muscle and liver but also brain, and the actual concentrations of the phosphate compounds were determined in these three organs. Three groups of dogs were studied: first, 6 normal controls, fasted for 40 hours; second, 4 dogs, which received globin insulin for 1 week and standard insulin and sugar 2 hours before the tissues were removed; and third, 9 dogs depauperatized from 3 weeks to 3 months previously and receiving their last insulin 16 to 64 hours before the tissues were examined. Tissues were frozen *in situ*, removed, ground in liquid air and extracted with trichloroacetic acid. Inorganic phosphate, phosphocreatine, adenosinetriphosphate and total phosphates were determined. The significant changes are as follows: for the brain, insulin increased the total phosphate content, for muscle, insulin increased phosphocreatine, and for liver,

insulin diminished inorganic phosphate and total phosphate and pancreatectomy reduced total phosphates. Except for muscle phosphocreatine, neither insulin injections nor pancreatectomy produced statistically significant differences in the concentrations of phosphocreatine and adenosinetriphosphate [Aided by a grant from the John R Markle Foundation]

The volume and composition of air expelled from the lungs during explosive decompression. FRED A HITCHCOCK, ABRAHAM EDELMANN (by invitation), FREDERICK F SHEIDT (by invitation) and W V WHITEHORN (by invitation) *Laby of Aviation Physiology and Medicine, The Ohio State Univ, Columbus*. The technique for producing explosive decompression developed in this laboratory makes available a new method for investigation of respiratory problems. Using this technique, experiments are under way designed to determine directly the volume and composition of residual air. Subjects are kept in the decompression chamber at a barometric pressure of 522 mm of mercury until respiratory equilibrium is established. An alveolar sample is then taken by the usual method. With the thoracic cage still in the position of maximal exhalation the barometric pressure is reduced by explosive decompression to about 261 mm of mercury. Since the pressure is reduced to one half its original value, the volume of the air contained in the lungs and respiratory passages doubles, and if the position of the thoracic cage remains unchanged, the volume expelled should just equal the volume remaining in the respiratory tract. Values obtained in this way are consistently larger than those obtained on the same subjects by dilution methods. This discrepancy is probably due to the fact that the sudden reduction of barometric pressure causes gases (chiefly carbon dioxide and water vapor) to diffuse rapidly into the alveolar spaces. It also seems likely that the volume of the nasal sinuses is more accurately measured by explosive decompression than by the dilution methods.

Analysis of the last air to leave the lungs after explosive decompression invariably shows a higher per cent of CO₂ than the alveolar air collected just before the explosion [Work done under contract with the Office of Scientific Research and Development]

Stressful psychomotor performance and adrenal cortical function in man HUDSON HOAGLAND, GREGORY PINCUS, and FRED ELMADJIAN (by invitation) *Worcester Foundation for Experimental Biology, Shrewsbury, Mass* (Read by title). We have previously demonstrated that the output of 17-ketosteroid is enhanced by a variety of stressful acts including the operation of pursuit-meters and we have found a relationship between the magnitude of the "stress output" of 17-keto-

steroids and fatigability of the individual (Pincus & Hoagland *J Av Med* 14, 173, 1943) Dougherty & White (*Endocrinology* 35, 1, 1944) have found that a drop in the lymphocyte count results from the action of adrenal cortical hormones in animals and we have shown that stress in normal mice results in a lymphocytopenia which is absent after removal of the adrenals (Elmadjian & Pincus *Endocrinology* 37, 47, 1915).

Effects on the efficiency of performance of mixtures of air low in oxygen have been determined in one hour runs on six normal persons operating our pursuit meter. The lymphocyte count falls with the experimental stress. We find that the lower the drop in lymphocytes the greater the decline in efficiency of performance as scored on our pursuit meter and measured by decline in the "fatigue ratio". The correlation coefficient relating this fatigue measure to the lymphocyte change is $r = 0.441$ with a P of < 0.01 .

The stress increases the output of 17-ketosteroids as it lowers the lymphocyte count.

The effects of the antihistamine compound pyribenzamine on colonic activity in unanesthetized dogs. JUSTIN HOEKSTRA (by invitation) and F R STEGGERDA *Dept of Physiology, Univ of Illinois, Urbana, Illinois* (Read by title). In dogs with colons made permanently opaque to x-rays with Thorium Dioxide (Thorotrast), studies were made to test the effects of the antihistamine compound Pyribenzamine on normal colonic motility and its antagonistic effects to known amounts of Histamine Phosphate. Simultaneously, radiograms were taken and actual pressure changes within the colon were measured and recorded by means of an open tipped catheter inserted into the lumen of the lower colon via the rectum. These pressure differences were recorded on a smoked drum with a water manometer. The administration of the drugs was made by intracardial injections.

The results of 43 different experiments on 6 dogs indicate that the antihistamine compound in doses from 0.1 to 2.9 mg/kg causes an increase in colonic activity in proportion to the amount given, either by increased amplitude or frequency or a combination of both. Usually, there also occurred an increase in muscular tone.

To test the antagonistic effects of the antihistamine compound, the contractive effect of 10 to 30 gamma of Histamine was first observed, and then at various time intervals after antihistamine had been given, the same dose of Histamine was repeated. The results show that with doses of antihistamine up to 0.5 mg/kg, there occurs no protective effect against Histamine. However, with larger doses (1.5 to 2.5 mg/kg), inhibitions to Histamine are recorded which may last as long as 50 minutes, but with the larger doses of anti-

histamine, there occurs labored breathing and marked salivation

Metabolism of dehydroisoandrosterone M M HOFFMAN and M L DESBARATS (introduced by J S L Browne) *From the McGill Univ Clinic, Royal Victoria Hospital, Montreal, Canada* Four grams of dehydroisoandrosterone were administered orally to two male rabbits. The neutral ether soluble fraction of the acidified, boiled urine contained 890 mg of 17-ketosteroids. Chromatographic analysis of this fraction resulted in the isolation of Δ^5 -androstadienone-17 (434 mg), etiocholanol 3(α)-one-17 (38 mg), dehydroisoandrosterone (65 mg) and Δ^5 androstenediol-3(β), 17(β) (90 mg). It is considered likely that the Δ^5 -androstadienone-17 is an artefact arising from the dehydration of some other steroid, as yet unidentified, during the course of acid hydrolysis. Etiocholanol-3(α)-one-17 has generally been considered to represent a metabolite of a Δ^4 -3 ketosteroid such as testosterone, the present experiment indicates that it may also be derived from a Δ^5 -androstenediol-3(β), 17(β) establishes the fact that the ketone group at C-17 in the neutral ketosteroid, dehydroisoandrosterone, may undergo the same metabolic transformation as the corresponding group in the phenolic ketosteroid, oestrone.

Calcium in gastric mucus FRANKLIN HOLLANDER and FRANCES U LAUBER (by invitation) *Gastro-Enterology Research Lab, The Mount Sinai Hospital, New York City* Mucus was collected from dogs' Heidenhain pouches by contact stimulation with emulsions of eugenol (5%) and mustard oil (1%). Calcium content, electrometric pH, and a qualitative evaluation of viscosity were recorded for each specimen. Calcium concentrations ranged from 7.7 to 13.3 mg/100 ml ($N = 86$ specimens), 72% of these fell between 9.0 and 11.0 mg/100 ml. The mean was 10.04 ± 0.11 (σ_m). For eugenol specimens alone the mean was 9.76 ± 0.18 , and for mustard oil 10.31 ± 0.10 . The difference between these two means is without statistical significance, in spite of the fact that the mustard oil specimens were all fluid whereas the viscosity of those collected with eugenol varied extensively. For eugenol alone, the calcium content seems to vary with the viscosity, but the correlation is spurious. The pH was invariably above 7.4, its correlation with calcium content is poor. Serum calcium values were obtained in some instances, these averaged 11.5 ± 0.25 ($N = 6$) and were always greater than the simultaneous mucus values. Treatment with 0.1 N HCl *in vitro* extracts all of the calcium from the insoluble portion of the mucus. [Aided by grants from the Altman Foundation and Wyeth, Inc.]

Fatal doses and respiratory minute volumes in rabbits intravenously injected continuously with NaCN RICHARD G HORTON (introduced by Boris

B Rubenstein), *Medical Division, Edgewood Arsenal, Maryland* Continuous injections of NaCN were given until respiration had almost ceased. No important differences were found in comparing thirty-three (33) unanesthetized and forty-four (44) anesthetized (Dial-Urethane, 0.5 cc/kg) rabbits. Injected at 0.167 mg/kg/min, mean fatal doses agreed with the acute fatal dose of 1.4 mg/kg. At 0.069 mg/kg/min mean fatal doses were 2.5 mg/kg, indicating, at this injection rate, a detoxication rate of 0.027 mg/kg/min, a rate previously estimated at this and lower injection rates by Pratt, Horton, and Zierler in rabbits (unpublished) (O Bodansky, et al (unpublished) made similar studies in anesthetized cats).

Per cent respiratory changes in anesthetized and unanesthetized rabbits were similar. In both, initial respiratory stimulation was compensated by secondary depression so that minute volumes averaged throughout injection (300 cc/kg/min for anesthetized, 500 cc/kg/min for unanesthetized) were about the same as those preceding injection. Maximum minute volumes were nearly double preinjection values. Time to reach maximum minute volume was about 35% of the total time of injection at 0.167 mg/kg/min and nearer 60% at 0.069 mg/kg/min. In general, the sooner maximum minute volume was reached, the smaller was the fatal dose. The immediate increase in minute volume produced by small acute doses (0.14 mg/kg and 0.07 mg/kg) did not appear to be related to the individual fatal dose.

The phosphates and other compounds in the gastrocnemius muscle of scorbutic guinea pig S M HORVATH and D TEBBIE (by invitation) *The Fatigue Lab, Harvard Univ and the Boston City Hospital* It was noticed in earlier studies that guinea pigs on ascorbic diets showed signs of fatigability prior to the appearance of clinical signs of scurvy. Guinea pigs on an ascorbic diet were sacrificed after varying periods of time on this regime. These animals were anesthetized with nembutal and after the gastrocnemius were dissected free from the surrounding tissue, they were frozen *in situ* and removed. Analyses were made for water content, creatine, nitrogen, total and acid soluble phosphorus, phosphocreatine, adenosine triphosphate, glycogen and lactate.

For the first fifteen days on the ascorbic diet no definite alterations in the concentration of any of these compounds was noted. A sharp decrease of approximately twenty per cent in the concentration of acid soluble phosphorus, phosphocreatine, adenylyl-triphosphate, nitrogen and creatine occurred in the following period (up to 32 days on the ascorbic diet). There were a few exceptions to this general pattern and probably represent individual variations in the rate of development of scurvy. The changes in the concentration of lactate,

contraction

Relation of pulmonary ventilation to arterial oxygen saturation C S HOUSION (introduced by J L Lilienthal, Jr) *School of Aviation Medicine, U S Naval Air Station, Pensacola, Fla* (read by title) Under anoxic conditions, hyperventilation is known to increase arterial oxygen saturation. In this study an attempt was made to quantitate the relation of pulmonary ventilation to arterial oxygen saturation during anoxia. Ten resting subjects breathed 10.5 per cent oxygen in nitrogen at sea level, adjusting respiratory volume at various levels between 5 and 30 liters per minute. Oxygen saturation was measured by a Coleman Millikan oximeter, and in a number of cases the tensions of oxygen and carbon dioxide in arterial blood were determined directly in samples drawn through an indwelling arterial needle. Alveolar pressures were also determined. Arterial oxygen saturation was found to increase markedly with increasing ventilation. An increase of 2-3 l/m above the resting ventilation increased the arterial saturation by 10 to 20 per cent units. Doubling the resting ventilation increased the saturation by 20 to 30 per cent units, which was almost as large an increase as was obtained by any greater ventilation. The determined arterial oxygen tensions increased in direct proportion as ventilation increased. Alveolar determinations indicated that oxygen tension rises about 1.5 times as fast as carbon dioxide falls, with increasing ventilation. It is emphasized again that arterial saturation cannot be predicted from knowledge of the inspired oxygen tension unless other conditions (such as ventilation) are known. Clinical application of anoxia (such as the anoxemia test for coronary insufficiency) should be based therefore on arterial oxygen saturation rather than on a fixed percentage of inspired oxygen. *[The opinions or assertions contained herein are the private ones of the writers and are not to be construed as official or reflecting the views of the Navy Dept or the naval service at large.]*

The effect of adrenalectomy in rats on urinary non-protein nitrogen during forced-feeding and during fasting DWIGHT J INGLE and ELIZABETH A OBERLE (by invitation) *Research Labys, The Upjohn Company, Kalamazoo, Michigan*. In experiment 1, male rats (300 gms initial wt) were adapted to the forced-feeding of a medium carbohydrate diet for 2 weeks. All of the animals were given a solution of 1 per cent sodium chloride to drink during all phases of the experiment. Eight rats were adrenalectomized and 7 were sham-operated. During the 1st post-operative day the

feeding the urinary nitrogen of the adrenalectomized group did not decrease below the pre-operative level or the level of the control group. During a 10 day fast the adrenalectomized animals excreted as much urinary nitrogen as their controls.

In experiment 2, a medium protein diet was force-fed but the other experimental conditions were identical with those of experiment 1. The results paralleled those of experiment 1 up to the last two days of fasting when the level of urinary nitrogen of the sham operated rats was definitely higher than that of the adrenalectomized rats.

Treatment of impending hemorrhagic shock with an antihistamine agent. RAYMOND C INGRAHAM and HAROLD C WIGGERS *Dept of Physiology, College of Medicine Univ of Illinois, Chicago*. It seems possible that some of the tissue damage developing in hemorrhagic hypotension and leading to the irreversible shock state may be due to the release of histamine. With this idea in mind, the effectiveness of one of the new antihistamine agents was explored.

Dogs subjected to the standardized shock producing procedure (90 min of hemorrhagic hypotension at 10 mm Hg) pass from an impending to an irreversible shock state in 77% of all experimental attempts.

In the present series of 16 animals, 15 mg/kg of B-dimethylaminoethyl benzhydryl ether (Benadryl) was administered subcutaneously 30 min before hemorrhaging. This dose was supplemented 1 hour later with an additional 5 mg/kg.

The mortality rate in this series was unaltered from the controls (75%). The average survival time of the shocked animals also was not changed. The characteristic criteria signifying the transition from impending to irreversible shock were observed in all animals.

The conclusion is reached that Benadryl, an effective antispasmodic, is ineffective in delaying the onset of irreversible hemorrhagic shock. These findings suggest that the liberation of histamine may play no role in the production of the irreversible tissue damage of hemorrhagic shock.

Phospholipids in the visual cycle MARY ISHIMOTO (by invitation) and GEORGE WALD *Biological Labys of Harvard Univ, Cambridge, Mass*. The exposure of dark-adapted retinas of frogs or cattle to light liberates, in addition to retinene, large amounts of phospholipid. After drying retinas by grinding with anhydrous sodium sulphate or by lyophilization, their free phospholipids can be extracted by Soxhletting with benzene in the dark. This does not attack rhodopsin. After two hours of

8

uch extraction, only negligible amounts of phospholipid still appear. On bleaching the residual material, new phospholipid is liberated, in many times the molar equivalent of the liberated retinene.

The retinene and phospholipid liberated on bleaching are not bound together. They can be separated by chromatographing on magnesium oxide, or by precipitating the phospholipid with acetone magnesium chloride.

A mixture of phospholipids is liberated. About 60-70 per cent of the phosphorus is associated with choline, and about one-fifth of this appears to be sphingomyelin.

The bleaching of rhodopsin which has been extracted from the retina yields retinene, but no phospholipid. Conversely, the extraction of dried retinal tissue with benzene in darkness for some 20 hours removes almost all phospholipid, though no retinene. At any point in the latter process before all phospholipid has been removed, bleaching results in a special liberation.

It appears therefore that in the structure of the retinal rods, a mixture of phospholipids is intimately associated with rhodopsin, so as to be liberated on its bleaching. This association is broken by the separate extraction of either rhodopsin or phospholipid.

Some ionic and osmotic equilibria of the erythrocyte. M. H. JACOBS and DOROTHY R. STEWART (by invitation) *Dept. of Physiology, Univ. of Pennsylvania, Philadelphia*. In dealing with a variety of ionic and osmotic equilibria of the erythrocyte it has been found useful instead of treating each case separately to determine the equilibrium conditions for a single case so complex and general as to include within itself all the others. If erythrocytes initially containing known amounts of water, non-penetrating anions, cations and neutral molecules and hemoglobin in all forms are equilibrated with a large volume of external solution containing any known possible combination of penetrating and non-penetrating anions, penetrating and non-penetrating cations, penetrating and non-penetrating neutral molecules and protein in all forms, it is possible, with certain reasonable simplifying assumptions and a knowledge of the titration curve of the cell contents, to obtain equations for the equilibrium conditions with respect to the water content, internal pH, and state of ionization of the hemoglobin of the cells, together with the final distribution of all the various ions and solute molecules present in the system. For special cases in which some or many of the possible constituents of the most general system are missing the equations assume relatively simple forms. The general applicability of this method of treatment is illustrated by experimentally deter-

mining typical situations: (a) fragility determinations in salt solutions, (b) "colloid-osmotic" hemolysis, (c) "anomalous osmotic swelling", (d) unequal distribution of ammonium salts, and (e) temporary swelling in the presence of free ammonia.

The kinetics of visual processes. I Critical flicker frequency as a function of intensity. THEODORE LOUIS JAHN *Dept. of Zoology, State Univ. of Iowa, Iowa City* (Read by title). The following equation for visual critical flicker or fusion frequency (F) as a function of intensity (I) has been derived on the basis of the photochemical theory

$$F = k_4 p [L_1 I(a - x)]^q (F_{\max} - F)^r / C$$

where k_4 is the velocity constant of the $L \rightarrow T$ reaction, q probably pertains to the mechanism whereby the active photo-product is utilized by the sense cells, the quantity to the power r describes the mechanism whereby the sensation of flicker approaches a maximum when the frequency of repetitive equivalent stimuli is increased, and the other symbols have their usual meanings. The fundamental assumption is that for detection of flicker the rate of the $L \rightarrow T$ reaction must reach some constant given value.

This equation has the same general form as that of Hecht. However, the parameters of the two equations have quite a different significance. The new meanings assigned to the parameters allow much more freedom in adjusting the equation to fit experimental data, and all known flicker data can be fitted reasonably well.

The new equation predicts the observed shift in flicker-intensity curves with changes of temperature and with change of light-dark ratio, and it makes no assumptions regarding the photochemical cycle which contradict the chemical evidence.

The kinetics of visual processes. II Brightness discrimination and visual acuity as functions of intensity. THEODORE LOUIS JAHN *Dept. of Zoology, State Univ. of Iowa, Iowa City* (Read by title). The following equation has been derived for brightness discrimination ($\Delta I/I$) and visual acuity (α) as functions of intensity

$$\Delta I/I = \alpha = (C/L_1 l - w)/k_4 X^2 t$$

where k_4 is the velocity constant of the $L \rightarrow T$ reaction, l is the concentration of L , w is the equilibrium quantity of active photoproduct, k_4 is the velocity constant for the conversion of inactive photoproduct to visual purple, x is the concentration of inactive photoproduct, and t is the duration of the flash.

The fundamental assumption is that in brightness discrimination, in order for the difference to be detected, the total rate of the $L \rightarrow T$ reaction

These equations can be fitted to all existing data and are not in conflict with the available chemical evidence

The kinetics of visual processes III Dark adaptation THEODORE LOUIS JAHN *Dept of Zoology, State Univ of Iowa, Iowa City* If the concentration of visual purple is represented by z , that of visual yellow by y , and visual white by x , and if we ignore the conversion of visual yellow to visual white during dark adaptation and assume that regeneration from visual yellow is mono- or bimolecular and that regeneration from visual white is autocatalytic, we may write the following equation for the regeneration of visual purple

$$dz/dt = k_1 x^n + k_2 y z$$

From this equation z may be obtained as a function of time in the dark (t)

If the amount of visual purple is calculated from available dark adaptation data, the resulting curves vary from an almost pure mono- or bimolecular curve following slight light adaptation to an almost pure autocatalytic curve following intense light adaptation. Intermediate degrees of adaptation result in combinations of the two types. These curves can be matched with those for the integral of the above equation. This explanation assumes that mild adaptation converts most of the visual purple into visual yellow and intense adaptation converts most of it into visual white (data of Wald and Clark, and Haig)

Complete regeneration from visual white is very slow (as low as 35 per cent in 40 minutes, data of Hecht, Haig, and Chase). The latter part of this regenerative process does not fit the autocatalytic curve. The simplest explanation seems to be that vitamin A leaves the rods via the blood and is then returned very slowly.

Silicones and blood coagulation L B JAKES, E FIDLAR (by invitation), E T FELDSTED (by invitation), and A G MACDONALD (by invitation) *Dept of Physiology, Univ of Toronto, Toronto, Ont, and Dept of Physiology, Univ of Manitoba, Winnipeg, Man* The use of a silicone coating (General Electric Dri-Film) on glassware and needles gives a surface which preserves blood from clotting for several hours and which preserves the platelets from agglutination and disintegration for at least half an hour. By the use of this material it is possible to obtain normal plasma without the use of anticoagulants. Such plasma clots in 20-40 minutes in glass, 2-4 hours in silicone, the clotting time depending in part on the number of platelets remaining in the plasma. Contamination with traces of damaged tissue will clot this plasma rapidly.

It is concluded that the acceleration of clotting due to the character of the surface is caused by the effect of surface on the platelets and that this effect is not observed with the surface presented by the silicone. The clotting of this plasma by damaged

tissue is uninfluenced by the nature of the surface [*Aided by a grant from the John and Mary R Marille Foundation*]

Effect of intermittent exposure to a simulated altitude of 30,000 feet on memory in guinea pigs A V JENSEN (by invitation), R F BECKER and W F WINDIE *Inst of Neurology and Dept of Anatomy, Northwestern Univ Medical School, Chicago* (Read by title) Fifteen young adult male guinea pigs were subjected to daily (except Sunday) 6 hour exposures to a simulated altitude of 30,000 feet. Nine control animals were provided. Previous to the exposures all the animals were taught a simple alternation maze problem.

After 100 hours exposure, all the animals were tested for retention of learning. No significant difference between experimental and control animals was found. After 150 hours, a group of 4 experimental and 2 control animals, selected randomly without regard to performance scores, was retested. The controls were found to be letter-perfect, the experimentals required extensive retraining. After 200 hours, all the remaining animals were retested. Five out of six of the controls showed perfect retention, as against 1 out of 8 of the experimentals. After 250 hours, 4 experimentals and 5 controls were retested. The controls were letter-perfect. None of the experimentals was able to even relearn the problem in 20 trials, although at 200 hours they had all relearned it in less than 10 trials.

At the end of each testing period groups of 4 experimental and 2 control animals were sacrificed for histopathological study of the brain [*Aided by a grant from the National Foundation for Infantile Paralysis, Inc*]

A mathematical analysis of pulse volume determinants KENNETH E JOCHIM, *Dept of Physiology, St Louis Univ School of Medicine* Previously reported experiments on a mechanical model of the circulatory system have shown that the pulse pressure depends on the pulse volume or systolic uptake of the elastic arterial system, and on the shape of the pressure-volume curve of this system. Regardless of wide variations in heart rate, peripheral resistance and the nature of the elastic system, the pulse volume remains equal to approximately 0.5 times the stroke volume.

If the mass and turbulence of the circulating fluid are neglected and an elastic system with a linear pressure-volume curve is used, the differential equation for the system can be solved for stabilized conditions and one can calculate the pulse volume and pulse pressure for any given values of heart rate, peripheral resistance and slope of the pressure-volume curve. Such calculations show that the value of the ratio $\frac{\text{pulse volume}}{\text{stroke volume}}$ is determined only by the product of the heart rate, the peripheral resistance and the reciprocal of the slope

of the pressure volume curve of the elastic system. This ratio varies only from 0.45 to 0.55 as the product mentioned above varies from 1.73 to infinity.

Experimental results show good agreement with these calculated values, and indicate that the mass and turbulence of the fluid and a non-linear pressure volume relationship do not significantly affect the $\frac{\text{pulse volume}}{\text{stroke volume}}$ ratio.

Reduction time of peripheral cutaneous blood as a means of evaluating fitness. J. RAYMOND JOHNSON, GEORGE B. RAY (deceased) and LOUISE H. RAY (by invitation). Although the reduction time of blood in the skin is subject to several possible physiological variables, it remains fairly constant at rest. During a mild form of stress, such as holding the breath, it decreases in normal healthy subjects, due largely, we believe, to redistribution of blood. Since such a reaction represents a compensatory adjustment in the body, it seemed possible that the extent of the reaction might serve as a valuable index in evaluating the fitness of an individual.

The per cent decrease in reduction time after breath holding, which we call the reduction time score, was determined in several different groups, representing varying degrees of fitness estimated on the basis of general health, activity, training, etc. Men who might be considered as normals, (1) medical students on an accelerated schedule, (2) medical students on a normal schedule, and (3) marines and naval aviators on active duty, showed, in that order, progressively greater scores, while men rejected or discharged from military service for physical reasons and hospitalized patients showed very low scores or even scores of opposite sign, depending on the degree of physical incapacity. Within the group of marines there was a significant correlation with the degree of training, and the naval aviators showed distinctly better scores before than after a flight. In following a number of hospitalized patients during convalescence from acute illness, operation, or traumatic injury, a close correlation has been found between degree of recovery and reduction time score. [Work done under contract with the Office of Scientific Research and Development.]

Certain influences affecting the cardiac recovery index of medical students. FREDERIC T. JUNG, LILLIAN E. CISLER (by invitation), and VELMA C. MILLER (by invitation). Dept. of Physiology, Northwestern Univ. Medical School, and Passavant Memorial Hospital, Chicago. The cardiac recovery index (CRI) obtained in this study was the resultant of three heart-rates counted under special conditions during recovery from a prescribed exercise. This was given at about 9 A.M. after a night spent in a hospital bed in preparation for determinations of basal metabolic rate and other

tests. Subjects of Group J were 30 Juniors (aged 21 to 27), each was retested exactly 7 days later. Group F consisted of 40 Freshmen (19 to 26), an average of 39 days (including 3 weeks of vacation) intervened between test and retest.

During the 7 days, Group J gained 0.02 kg. in mean weight, during the 39 days that included the vacation, Group F gained 0.53 kg. The mean CRI for J was 95.27 before, and 98.17 after the 7-day interval, the test-retest correlation coefficient $R = +0.92$ showed this test to be very reliable, and the gain of 2.90 points was found significant. The gain was ascribed to practice. For the F group, the mean CRI was 91.95 before, and 96.12 after the vacation, the R was $+0.60$, and the gain of 4.17 points was found significant. It seems logical to ascribe most of this gain to the vacation. [Aided by the Abbot Memorial Fund.]

Relation between breath holding and endurance in running, and the Harvard step-up test score. PETER V. KARPOVICH. AAF School of Aviation Medicine, Randolph Field, Texas. Forty-eight aviation students were given the following five breath holding tests: 1, after three deep inhalations; 2, after one full exhalation; 3, immediately after making 24 step-ups in one minute on a 20-inch bench; 4, while doing step-ups on a 10-inch bench; 5, while doing step-ups, on a 20-inch bench. In each test the breath was held as long as possible.

The same men also ran to exhaustion on a treadmill and were given the Harvard step-up test.

The coefficients of reliability for each of the seven tests are statistically significant. The coefficients of correlation of the breath holding time after inspiration with the other four breath holding tests are statistically significant. The coefficients of correlation between breath holding tests on the one hand and the treadmill running time and also the Harvard step up test score on the other hand are statistically not significant.

Breath holding cannot be considered a test for predicting endurance in running or for predicting the Harvard step up test score.

Mechanical efficiency of the heart in experimental heart failure. L. N. KATZ, W. WISE (by invitation), J. MEYER (by invitation), B. LENDRUM (by invitation), and K. JOCHIM. Cardiovascular Dept., Research Inst., Michael Reese Hospital. Our previous observations that when the cardiac output is kept constant the mechanical efficiency of the failing heart does not decline, were subjected to re-investigation. Data were obtained during the control and failure periods on previously described heart-lung and isolated heart preparations. The efficiency of each preparation was determined several times during both the control and failure periods. These data are summarized in the following table of averages.

Preparation	Number of preparations	Mechanical efficiency	
		Control period	Failure period
Heart-lung	11	3 6%	4 1%
Isolated heart	8	3 7	3 9

It is apparent that there is no significant difference in the efficiency between the control and failure periods

Endocrine glands and gastric secretion J KAULBERSZ, T L PATTERSON, D J SANDWISS and H C SALTZSTEIN (by invitation) *Dept of Physiology, Wayne Univ College of Medicine and the Lab of Experimental Surgery, Harper Hospital, Detroit, Mich* In our previous studies related to the preparations of urogastrone from dogs deprived of some of the endocrine glands (Science, 102 530, 1945) the influence of different extracts was tested on gastric secretion The secretory depressant in urine of each of the four series of dogs oöphorectomized, thyroidectomized plus oöphorectomized, hypophysectomized, and normals exhibited different degrees of potency Extracts from normal and from thyroidectomized plus oöphorectomized dogs exerted the highest inhibitory action, those from hypophysectomized animals the lowest Following removal of the pituitary the extract even increased gastric secretion after histamine

These observations led to a study of gastric secretion on the different series of dogs Gastrotomies were performed on three hypophysectomized and three thyroidectomized plus oöphorectomized animals and gastric secretion of each of these was stimulated by histamine Urine extracts of normal and operated dogs were administered in order to study their influence on secretion and acidity of gastric juice

The averages in milliequivalents of free HCl secreted after histamine injection alone varied greatly, therefore it was difficult to conclude how much the secretion and acidity was changed as compared to the normal Urogastrone from normal dogs inhibited less frequently gastric secretion of the thyroidectomized plus oöphorectomized than of the normal, whereas extracts from these operated animals diminished the HCl output more frequently Urine preparations from the hypophysectomized group were particularly active on animals deprived of thyroids and ovaries, also dogs without the pituitary were more susceptible to the stimulatory influence of hypophysectomized extracts than the normal

Flicker fusion frequency thresholds during positive acceleration GEOFFREY KEIGHLEY (by invitation) and WILLIAM G CLARK *William G Kerckhoff Lab, California Inst of Technology,*

Pasadena, and the Dept of Aviation Medicine, Univ of Southern California, Los Angeles (Read by title) Monocular, flicker fusion frequency thresholds have been determined on 10 subjects, under positive acceleration on a centrifuge

The results are expressed as differences in cycles per second (C P S) between the mean thresholds at rest, immediately before a run, and those found during acceleration

At low accelerations (2.2-3.2 G, mean 3.0 G) causing no visual disturbances, 53 runs were made Most lasted 45 seconds The differences between thresholds ranged from +1.3 C P S (fusion frequency higher during acceleration) to -1.6 C P S, and were distributed fairly equally about the zero baseline, 21 were positive, 32 negative The range ± 1 C P S includes 48 of the results 34 are in the range ± 0.5 C P S These figures show no changes in the flicker fusion thresholds

At higher accelerations (2.8-4.8 G, mean 4.0 G) 34 runs were made, lasting up to 60 seconds with negative pressure over the eyes to restore vision (Lambert, unpublished) At these accelerations without the negative pressure, there was dimming or loss of peripheral vision or blackout No fusion frequency was higher during a run The greatest difference in fusion frequency between rest and acceleration was -3.9 C P S The range 0 to -2.0 C P S includes 21 of the 34 results The differences are all negative, more spread out than at lower accelerations, and the range is greater At these higher levels of accelerations, with vision restored, the fusion frequency of flicker is lowered [The work was done under a contract with the Office of Scientific Research and Development]

The human tolerance for potassium NORMAN M KEITH and ARNOLD E OSTERBERG (by invitation) *Mayo Clinic, Rochester, Minnesota* In 1941 the authors demonstrated that as much as 80 to 100 mg of potassium per kilogram of body weight, in the form of a potassium salt, could be ingested at one time without demonstrable toxic effects In these experiments distinct alterations were observed in the clearance of potassium by the kidneys and in electrocardiographic tracings We have since then made similar observations on five normal subjects after the ingestion of 27 to 43 mg of potassium per kilogram of body weight, as potassium bicarbonate The effect of the smaller dose was clearly discernable in the electrocardiograms and renal clearances of potassium The urinary volume was increased and the renal clearance of potassium rose to between 29 and 67 cc The electropotential changes in the heart and excretory alterations in the kidneys were associated with a rise of 2 to 4 mg in the concentration of potassium in the blood serum in four subjects, in the fifth subject an initial high normal concentration, 20.3 mg, was sustained A control experiment with the ingestion

vealed no significant changes in electrocardiograms or renal clearance of potassium. Therefore the ingestion of approximately 35 mg of potassium per kilogram of body weight can produce demonstrable alterations in cardiac and renal functions. Further experiments are contemplated to ascertain whether the ingestion of a similar amount of potassium present in our daily food will produce similar effects on the heart and kidneys.

The striking inherent tonus of the deafferented central pupilloconstrictor neurons. By ALLEN D. KELLER, *Dept of Physiology and Pharmacology, Baylor Univ College of Medicine, Houston, Texas*. It has generally been assumed that the multitudinous factors concerned in determining the size of the pupils operate around an inherent tonus of the pupilloconstrictor nerve cells. This assumption is correct because it has been found that these cells do discharge impulses continuously when they are completely deafferented by two transections of the brain stem, one placed above and the other below the oculomotor nuclei and nerves. Under these conditions, the pupils remained permanently and markedly constricted except when they were dilated by sympathetic efferent impulses, during spurts of somatic activity, i.e., struggling movements. Unilateral section of the cervical sympathetic trunk in the neck prevented dilation of the pupil on that side under these conditions. Atropine applied to one eye resulted in dilation of that pupil, the other one remained constricted.

That the discharge of the pupilloconstrictor impulses is due to an inherent mechanism within the cell bodies seems reasonably certain. The possibility that the discharge is due to an irritative stimulation of these cells by factors incident to the transections seems unlikely because the condition has persisted in a preparation that has been maintained for 11 weeks after operation. The only other possibility of extraneous stimulation would be by way of the blood stream.

Effects of alterations in the arterial tensions of carbon dioxide and oxygen on cerebral blood flow and cerebral oxygen consumption of normal young men. S. S. KERRY (by invitation) and C. F. SCHMIDT, *Dept of Pharmacology, Univ of Pennsylvania, Philadelphia*. By means of the nitrous oxide method previously reported by the authors (*Am J Physiol*, 143: 53, 1945) quantitative measurements were made of the changes in blood flow and oxygen consumption in the brains of unanesthetized young men during active and passive hyperventilation with room air, inhalation of 5 per cent and 7 per cent CO_2 with 21 per cent O_2 , of 85-100 per cent O_2 and of 10 per cent O_2 .

Both active and passive hyperventilation were accompanied by consistent decreases in cerebral blood flow averaging 32 per cent and 36 per cent

associated with a consistent increase in cerebral blood flow averaging 75 per cent. High oxygen led to a 12 per cent decrease and 10 per cent O_2 to a 37 per cent increase in cerebral blood flow. These changes are all statistically significant. There was no significant change in cerebral oxygen uptake except in active hyperventilation, during which it underwent a consistent increase averaging 15 per cent. Cerebral vascular resistance (calculated from cerebral blood flow and direct mean arterial blood pressure) was increased by hyperventilation and high O_2 inhalation and decreased by low O_2 and increased CO_2 . Both cerebral blood flow and cerebral vascular resistance showed good correlation with arterial pH, pCO_2 and pO_2 . [Work done under contract with the Office of Scientific Research and Development.]

Experimental human starvation—general and metabolic results of a loss of one fourth the body weight in six months. ANCEL KEYS, *Laby of Physiological Hygiene, Univ of Minnesota, Minneapolis, Minnesota*. Thirty-four normal young men resided in the laboratory on a standard regimen. Caloric balance required 3200 Cal daily during 3 months of control studies. For 167 subsequent days they subsisted on a European type of famine diet averaging, daily, 1790 Cal, including 22 grams of fat, 49 grams of protein, 1.29 mg of thiamine, 0.71 mg of riboflavin, 20.7 mg of niacin and 29.8 mg of iron. During this time they lost from 27 to 65 pounds, representing an average of 24 per cent of their original weight. The clinical picture closely simulated that seen in the less fortunate areas of Europe liberated in the Spring of 1945. Prominent were muscular weakness, edema, bradycardia, cyanosis, decreased tendon reflexes, depression and sensations of cold and unremitting hunger. Signs of vitamin deficiency were absent or equivocal. There was, on the average, a 22 per cent decrease in blood hemoglobin concentration, a 33 per cent decline in basal pulse rate and trivial declines in arterial blood pressure, body temperature and plasma protein concentration (-10 per cent). The basal oxygen consumption, in cc per minute, averaged 229, 185, 155, 144 and 140 in the control period and in the fifth, thirteenth, twentieth and twenty-third weeks, respectively. The total decline of 39 per cent in basal metabolism corresponded to a decrease of 11 per cent in surface area and of 41 per cent in "active tissue," defined as total weight less bone, fat (from body density), and extracellular water (from thiocyanate dilution). [This work was supported in part under a contract with the Office of Scientific Research and Development. Support from other sources will be acknowledged in final publication.]

Effects of deceleration on the electrocardiogram (lead II) in the cat in the supine position. HARRY

D KINGSLEY (introduced by Herman S Wigodsky) *AAF School of Aviation Medicine, Randolph Field, Texas* Thirty cats anesthetized with numbutal were exposed in the supine position to high decelerative forces ranging from 500 to 1200 g. Continuous recordings of Lead II on an electrocardiograph were made. In order to study vagus effects, three groups of 10 animals were used: Group I—no vagal interference, Group II—bilateral vagotomy prior to drop, Group III—0.15 mg physostigmine per kilo intravenously prior to drop.

In surviving animals, all EKG changes returned to normal within 15 minutes following deceleration. Three animals in Group III expired within an hour following deceleration. There was universal depression and inversion of T-waves in all experiments. These returned to normal in 60 to 90 seconds following impact. The degree of inversion was slightly greater in Group II. Rhythm changes, premature ventricular contractions with pulsus bigeminus occurred in 3 animals in Group I, and 4 animals in Group III. Group III animals that expired showed ventricular fibrillation, complete heart block, and S-A nodal bradycardia. No rhythm changes were observed in Group II. The T-wave changes together with frequent depression of the S-T segment were of the type common in experimental coronary occlusion.

All animals in Group II showed increases in heart rate, whereas the majority of animals in Groups I and III showed marked slowing.

The evidence indicates that there is marked transient EKG disturbances as a result of abrupt deceleration. The vagus has a marked effect on the production of arrhythmias and slowing. The parasympathicomimetic action of physostigmine had no apparent effect on the EKG in this series.

Blood studies in anaphylactic shock in dogs
J S KIRK (by invitation), O O STOLAND, C DOUGHERY (by invitation) and GEORGE BOONE (by invitation) *The Univ of Kansas, Lawrence, Dept of Physiology* Sedimentation rate studies were made on dogs sensitized to horse serum before and after shock. The sedimentation rate was observed to decrease during shock. An equivalent amount of horse serum injected into control dogs did not produce this effect. Interference with the return of lymph to the veins by ligation or cannulation of the thoracic duct tends to prevent this decrease of sedimentation rate in anaphylactic shock.

Hematocrit and red blood cell studies on both arterial blood and portal blood were made both before onset of shock and during early stages of acute shock. A significant increase in both hematocrit and red blood cell count was recorded in portal vein blood. No significant alteration of RBC counts and hematocrit in arterial blood occurred. White blood cell count decreased consistently in both arterial and portal blood.

Lymph flow from the thoracic duct was observed to increase during shock as has been recorded by many investigators.

Survival time and metabolic rate of starving rats MAX KLEINER *College of Agriculture, Univ of California Davis* Female rats 100 days old were starved at constant environmental temperatures. At 38°C all rats died within the first day. At 35°C 5 rats died on the first two days and 12 rats survived on the average 15 days, as did a group of 7 rats starving at 30°C. During starvation to death at 35°C the total weight loss amounted to 35 per cent of the initial body weight, starvation at 30°C produced a weight loss of 44 per cent. During the starvation at 35°C the respiratory quotient rose from an average of 749 on the first day to 883 on the last day before death. At the same time the metabolic rate decreased from 22.5 ± 0.6 kcal per rat, or 114 ± 3 kcal per kg body weight, to 9.6 ± 0.6 kcal per rat, or 81 ± 4 kcal per kg body weight. The rats starving at 30°C lowered their metabolic rate from 128 ± 2 kcal per kg body weight at the start to 62 ± 3 kcal per kg on the last day.

Raising the environmental temperature from 24 to 30°C prolongs the life of starving rats, raising the temperature further to 35°C does not prolong life nor does it lower the level to which the rats decrease their metabolic rate during starvation.

Body temperature and cutaneous sensitivity to tingling and pain N KLEITMAN and A RAMSAROOP (by invitation) *Dept of Physiology, Univ of Chicago* Tetanizing current was delivered from an inductorium to the volar surface of the terminal phalange of the middle finger, and the threshold to tingling and pain determined in an ascending manner. A forenoon test period comprised eight series of trials run on each of two subjects in the course of six hours. In each series, during the five minutes of testing, there was a gradual rise in sensitivity to tingling. This was also true of pain, but only when sensitivity was low.

The results obtained in 13 forenoons in one subject and 9 in the other showed a direct relationship between sensitivity to tingling and pain and the oral temperature at the time of the testing. In general, as the temperature rose in the course of the forenoon (from a mean of 97.51 degrees F to 98.29 in one subject and from 97.81 to 98.69 in the other), the cutaneous sensitivity also increased. When relaxing in the sitting position for one hour caused a fall in body temperature, there was a corresponding decrease in sensitivity, while subsequent standing up for one hour, if it raised the body temperature, also led to increased sensitivity.

The changes described were all statistically significant, more so for body temperature and sensitivity to tingling than for sensitivity to pain.

Evidence of a synergism between pyribenzamine HCl and sympathetico-mimetic drugs in

humans GEORGE F KOEFF, CARL E ARBESMAN (by invitation), and ALFRED LENZNER (by invitation) *Depts of Physiology and Medicine, Univ of Buffalo, School of Medicine, and the Buffalo General Hospital* Pharmacological studies using pyribenzamine HCl by Yonkman et al (Federation Proceedings, this issue) indicate that in experimental animals pyribenzamine in certain dosages appears to have an adrenergic potentiating effect. With this in mind certain studies on human subjects were made. Patients with bronchial asthma were given ephedrine only for the first test period, then pyribenzamine only, and finally pyribenzamine and ephedrine. Objective and subjective data revealed that in many instances the combined ephedrine and pyribenzamine therapy was more effective than either drug alone.

In another group of normal human subjects the effect of pyribenzamine on the response of the blood glucose to adrenalin was determined. The intravenous glucose tolerance curve as effected by pyribenzamine was also studied in humans. No significant variations were produced by pyribenzamine on the intravenous glucose tolerance curve. Further investigation of the effect of pyribenzamine directly on the liver glycogen stores, however, is indicated.

In allergic patients there is evidence that there is a synergism between ephedrine and pyribenzamine HCl. Attempts to demonstrate this synergism by changes in carbohydrate levels must be broadened.

The relation between tissue metabolism and physiological activity IRVIN M KORR (Formerly) *Dept of Physiology, New York Univ College of Medicine, New York*. In a previous report (Federation Proceedings 1941), based upon manometric studies of several mammalian tissues it was concluded that a) the (azide sensitive) Warburg-Keilin system participates slightly if at all in resting metabolism, whereas a major portion of the metabolism of the working cell traverses this system, and b) the same appears true of fluoride sensitive systems. Combined manometric, spectroscopic and analytical studies during 1942, mainly upon the cat's submaxillary gland, confirmed a) and b), and showed c) there was little or no aerobic glycolysis in the resting gland, but a rapid glycolysis appeared immediately upon stimulation (by acetylcholine), d) glycogen content, which remained constant for hours in resting slices, dropped precipitously upon stimulation, and e) metabolic changes induced by stimulation with acetylcholine were immediately reversed by atropine. f) Varied combinations of tissues and humoral agents showed that the changed metabolism was associated with activity of the tissue rather than with direct effect of the humoral agent upon metabolic mechanisms. E.g., pure secretin, now known to cause the release

of enzyme-free fluid by the pancreas did not affect the metabolism of that gland, while duodenal extract, containing also pancreozymin, which stimulates the elaboration of pancreatic enzymes, markedly increased the QO_2 of pancreas (but of no other tissue tested).

These observations support the hypothesis that 1) the sources of energy for work by the cell are different from those for cell maintenance, and 2) that the shift from the resting type of metabolism to the active is an integral part of the excitatory process. [Aided by grants from the American Philosophical Society, Ella Sachs Plotz Foundation and American Academy of Arts and Science.]

Frequency-intensity curves of normal, denervated and recovering gastrocnemii of the dog A J KOSMAN (by invitation) and S L OSBORNE *Dept of Physiology, Northwestern Univ Medical School, Chicago*. Frequency-intensity curves of the gastrocnemius muscle of the dog were determined before and for a six month period following the crushing of the tibial nerve. Using percutaneous methods of stimulation, threshold responses were determined over a frequency range of 0.1 to 10,000 c.p.s. In normal muscle an optimum frequency range occurs from 25 to 250 c.p.s. Discontinuities in the curve appear at 0.75 to 2.0 c.p.s. and at 2500 c.p.s. Following denervation, the optimum frequency occurs at 0.75 to 5 c.p.s. with a steep rise in the curve above 100 c.p.s. Accompanying the earliest stages of neurotization there is a shifting of the curve to the normal position with a marked rise in threshold intensities below 2.0 c.p.s. [Aided by a grant from the National Foundation for Infantile Paralysis.]

Warm-up period in physical exercise in relation to brain potential KROUSE, R. (by invitation) WICKWIRE, G. C. (by invitation) and W. E. BURGE, *Dept of Physiology, Univ of Illinois, Urbana, Illinois* (Read by title). The warm up period consisted of a few minutes of light exercise immediately preceding athletic contests such as wrestling, football, running, swimming, basketball, etc.

When one electrode was placed on the forehead as near over the motor area as the receding of the hair would permit and another on the forearm with a potentiometer in the circuit, the forehead was found to be positive to the forearm in the contestants while at rest with a potential difference of 15 to 25 millivolts. The light exercise during the warm up period increased the voltage anywhere from 50 to 75 millivolts. During the contests, the voltage continued to rise until fatigue and exhaustion set in and then the voltage dropped.

We had found in etherized dogs with trephined skulls (*Anesthesiology*, Vol 1, No 1, 1945) that the positive potential of the scalp fluctuated with the negative potential of the underlying brain cortex in a 1 to 8 ratio, so scalp potential may be

used as an index to brain potential, a rise or fall in the positive potential of the scalp indicating a rise or fall in the negative potential of the underlying brain cortex. Hence, if the relationship between scalp and brain potential for humans and dogs is comparable, the rise in the positive potential of the scalp of humans during the warm-up period as shown above indicated a rise in the negative potential of the underlying brain cortex, and the fall during fatigue and exhaustion indicated a fall in the brain potential.

Relationships between changes in muscle length, tone, tension, and pressure **HUGO KRUEGER** *Dept of Pharmacology, Univ of Tennessee, Memphis* Many dissimilar mechanical devices yield curves interpreted as "increases in smooth muscle tone". Supposedly these curves reflect the same manifestation of smooth muscle, but actually their only common property is an upward movement of the writing point. Thus, when weighed isolated strips of smooth muscle shorten, tone is said to increase although *the tension exerted remains constant* and no pressure is developed. When a water filled balloon, placed in a smooth muscle viscus, is distended at constant pressure, a shortening of the circular muscle is interpreted as an increase in tone although *the tension exerted decreases* owing to the relationship, $tension = pressure \times radius$ ($t = pr$). The pressure developed remains constant. If the balloon is connected to a water or Hg manometer, a decrease in length of the muscle is called a tone increase, while *the tension developed may increase or decrease* depending as before upon the relation $t = pr$, and the pressure increases as the radius decreases. If the balloon is connected to a stiff membrane manometer, the muscle cannot shorten appreciably (r remains constant) but the interpretation, increase in tone, is made when *the tension increases* and produces an increase in pressure.

Etymologically an increase in tone implies an increase in tension. Whether this definition of tone or some other is used, only misinformation develops if constant tension, decreased tension, increased tension, or indeterminate changes in tension are called tone increases. The phrases "tone" and "tone increase" should be replaced by measurements in muscle length, pressure and tension, or the other physical properties actually studied.

Glomerular filtration and renal plasma flow during renal and splanchnic nerve stimulation in dogs in relation to arterial hypertension **W G KUBICEK and F J KOTTKE** (introduced by M B

per cent decrease was observed in one instance. After two to four days of continuous stimulation renal flow and glomerular filtration returned toward normal, when, as usual, there was a persistent increase in blood pressure. In two animals in which chronic stimulation of the renal nerves produce only a moderate rise in blood pressure, the renal flow and glomerular filtration remained at low values for as long as two weeks. In one dog chronic stimulation of the splanchnic nerves produced initially a decrease of about thirty per cent in renal flow and glomerular filtration accompanied by an immediate rise in blood pressure to approximately 200/135 mm Hg which was maintained for about one week and then gradually fell toward normal.

Both renal and splanchnic nerve stimulation caused an increase in filtration fraction, presumably due to a greater constriction of the efferent than the afferent arterioles.

Splanchnic nerve stimulation brought about an immediate rise in blood pressure in contrast to the more gradual rise during renal nerve stimulation. This might be due to neurogenic vasoconstriction of the splanchnic bed as well as to adrenalin liberation.

Chronic stimulation of either renal or splanchnic nerves was accompanied by anorexia and vomiting. In some cases, with renal nerve stimulation, uremia, diarrhea, bloody stools and in one case, convulsions were observed.

The muscle membrane during contracture **S W KUFFLER** (introduced by R W Gerard) *Kanematsu Inst, Sydney, and Dept of Physiology, the Univ of Chicago* Contractures were set up in isolated single muscle fibres and the whole sartorius by constant current pulses and by drug application. Potential changes were recorded from the site of contractures.

Negative potential changes always occur at the site of origin of contractures. Like propagated muscle responses, contractures are initiated following a sufficient depolarization of the muscle membrane.

Contractures may develop following muscle impulses, which may fail to propagate fully from the region of their origin. In these preparations a transition can be detected from normal to "abortive" impulses and to a maintained negative potential change which may give rise to contractures without appreciably exceeding the potential level at which the preceding propagated responses had been set up. In fatigued, narcotized or injured muscles contractures can be set up directly following the depolarizing action of drugs or currents.

At the anode of constant currents, the setting

po assum app ica ion e e cetric time constant and the resting potential of the membrane are not significantly affected

The relationship between blood ketone levels and the storage of glycogen by the heart in acute experiments ROBERT W LACKEY (by invitation) and CARL A BUNDE *Dept of Physiology and Pharmacology, Southwestern Medical College, Dallas, Texas* Cardiac glycogen has long been known to be selectively increased in diabetes mellitus and in fasting We have recently reported a similar effect from fat feeding Each of these conditions results in ketonemia and in a depletion of insulin, one or both of which may be related to the deposition of glycogen in the myocardium This report deals with the production of ketonemia in acute experiments in adult rats by the administration of solutions of the sodium salts of butyric acid, beta-hydroxybutyric acid and acetoacetic acid by intravenous drip The solutions were administered over a period of four hours to animals anesthetized with sodium pentobarbital The animals were sacrificed one hour later at which time the blood ketone levels were still well above the normal value, and the store of glycogen in the heart was twenty-five to fifty per cent above control values There was no increase in liver glycogen By control experiments with a saline drip, it was shown that the anesthesia and operative procedures were without significant effect on cardiac glycogen

Since the experiments are of such short duration that a marked depletion of insulin seems unlikely, these findings appear to support the idea of a parallelism between ketonemia and glycogen deposition in the myocardium

Physiologic studies of man's gram tolerance in aircraft E H LAMBERT *Acceleration Laby, Mayo Aero Medical Unit, Rochester, Minnesota* This motion picture shows the procedures used in studies of g tolerance carried out on 42 men in a specially instrumented airplane and illustrates the sequence of symptoms which develop in airplane pilots and passengers exposed to positive acceleration

Pulling a g pattern similar to that used on the centrifuge, maintaining given accelerations for 10-15 seconds, pilots on the average experienced dimming of vision at 4.7 g, loss of peripheral vision at 5.1 g and blackout at 5.4 g This was 0.7 g units higher than their tolerance as passengers in the airplane and 1.4 g units higher than their tolerance on the Mayo centrifuge Factors causing the higher tolerance of pilots in the airplane included colder environmental temperature, more exciting circumstances of flying, crouching and the effort of pulling the control stick to execute the high g maneuver

Anti blackout suits afforded the same increase in

g tolerance to pilots and passengers in the airplane as to subjects on the centrifuge

The pattern of changes in the ear pulse, blood content of the ear, and pulse rate was the same for pilots and passengers in the airplane as for subjects on the centrifuge However, compensatory changes tended to occur one to two seconds earlier during exposure to g in the airplane

Conclusion The modern human centrifuge is a valid means for studying the physiologic effects of acceleration as encountered in aircraft and for developing methods of protection against these effects for pilots [*Work done under contracts with (1) United States Army Air Forces, Wright Field, Dayton, Ohio, and (2) the Office of Scientific Research and Development, National Research Council, Washington, D C*]

Direct determination of man's blood pressure on the human centrifuge during positive acceleration E H LAMBERT, and E H WOOD *Acceleration Laby, Mayo Aero Medical Unit, Rochester, Minnesota* Determination of the changes in arterial pressure during exposure to positive acceleration on the Mayo centrifuge was made in 20 men by puncture of the radial artery Pressures were recorded routinely by means of a resistance wire strain gauge manometer which activated a sensitive galvanometer and occasionally by a Hamilton manometer Pressures in the seated subject were measured with the wrist supported at head level or at heart level The various hydrostatic levels were determined from photographs of the subject taken prior to and during exposure to acceleration

For correlation with changes in arterial pressure simultaneous records were obtained of the subject's ear pulse, blood content of ear, heart rate, electrocardiogram, respiration, rectal pressure and reaction time to light signals in peripheral and central fields of vision

At the level of the eyes, the decrease in blood pressure per g increase in positive acceleration averaged 32 mm Hg systolic and 20 mm Hg diastolic During maintained acceleration the lowest pressure occurred in about 7 seconds and was followed by some recovery In general, with unimpaired vision the systolic pressure at eye level remained above 50 mm Hg and with complete loss of vision it was less than 20 mm Hg At the level of the heart (third interspace) the average decrease in pressure per g increase in acceleration was 4 mm Hg systolic and 0 mm Hg diastolic During recovery in g the pressure at heart level rose 20 to 70 mm Hg above the control value [*Work done under contracts with (1) United States Army Air Forces, Wright Field, Dayton, Ohio, and (2) the Office of Scientific Research and Development, National Research Council, Washington, D C*]

The electrosmotic transport of fluid through the walls of injured capillaries EUGENE M LANDIS *Dept of Physiology, Harvard Medical School, Boston, Mass* The electrosmotic transport of fluid through inert, and a few living, membranes (Mudd, *J Gen Physiol* 7 389, 1921) has been described but nothing is known concerning the effects of minute currents on the movement of fluid through the capillary wall It is interesting, therefore, to record that direct current can produce in single, injured capillaries an "electrosmotic absorption" of fluid, at rates depending on current intensity

Using the frog's mesentery and micro injection methods, one micropipette (5 to 10 μ in diameter) was introduced into a capillary, while a second (15 to 50 μ in diameter) was placed outside at a distance of 50 to 100 μ from the first Both pipettes, filled completely with Ringer's solution, were connected by 2 agar bridges to a suitable source of EMF If the internal electrode is made positive, currents of 1 to 10 microamperes (and a potential drop of 1 to 10 millivolts between electrodes) produces striking "electrosmotic absorption" of fluid in the mechanically injured area Erythrocytes, initially packed because of filtration of plasma, were dislodged and washed out of the injured capillary into the general circulation by the "absorbed" fluid which entered at rates between 0.1 and 3.0 μ^3 per μ^2 of capillary wall per second Interrupting the current was followed by resumption of the rapid filtration characteristic of capillary damage Reversing the polarity of the electrodes expedited both filtration and packing of erythrocytes

Central observations have shown that dye solutions in the injured capillary are washed out, as are erythrocytes, by colorless extravascular fluid and that the erythrocytes *in vivo* bear a negative charge as they do *in vitro* Quantitative observations are in progress to determine more accurately the relation which this "electrosmotic absorption" bears to injury itself and to determine whether or not electrosmosis can also affect the movement of fluid through the normal, and less permeable, capillary wall

The pharmacology of some new vaso-depressor compounds A M LANDS, ELEANOR RICKARDS (by invitation) and V LORAIN NASH (by invitation) *Dept of Pharmacological Research, Frederick Stearns and Co, Division of Sterling Drug Inc, Detroit, Mich* The pharmacological activity of a series of amines were investigated, particularly with reference to their effect on blood pressure Sympatol (1-(p-hydroxyphenyl)-2-methylamino-ethanol) has an epinephrine ratio of 316 The corresponding primary amine (A-15) has a ratio of 143 and tyramine a ratio of 68 The replacement of the methyl group on the N of Sympatol by larger alkyl groups makes the compound depressor in action

However, the structure of the alkyl substituent divides the series into 1) compounds causing a transient fall and 2) compounds causing a marked and prolonged fall in blood pressure The first includes those in which the N-alkyl group is propyl (A-14), butyl (A-12) and isobutyl (A-41), the second in which this group is ethyl (A-13), iso propyl (No 277), secondary butyl (A-44) or tertiary butyl (A-42) The isopropyl and secondary butyl derivatives are the most active No 277 has the most favorable therapeutic ratio

No 277, in intravenous doses of 0.5 mg/kg will lower the mean arterial blood pressure of dogs by 50-60 mm Hg for 1-4 hours The blood pressure of unanesthetized dogs is markedly reduced after intramuscular, subcutaneous or oral doses of 0.5-2.0 mg/kg Some reduction in mean arterial pressure has been observed for more than 8 but less than 24 hours

Acute toxicity was determined by intraperitoneal injection into albino mice Deaths were recorded for 72 hours following injection The approximate LD₅₀, in mg/kg, are A-14 300, A-12 150, A-41 220, A-13 550, No 277 360, A-42 250 and A-44 < 160

After discharge from sympathetic ganglion cells following preganglionic nerve stimulation. M G LARRABEE and D W BRONK *Johnson Foundation, Univ of Pennsylvania* We have previously reported that sympathetic ganglion cells discharge impulses for many seconds following brief stimulation of the preganglionic nerve at frequencies above 40 per second This is significant in interpreting afterdischarge and other evidence of prolonged excitatory states in the central nervous system, which are usually assumed to result from activity in chains of internuncial neurones Since sympathetic ganglia contain no interneurons, our observation demonstrates that afterdischarge can result from other mechanisms, such as persistence of environmental changes produced by presynaptic endings, or enduring changes in the cell body

Afterdischarge in single postganglionic axons from the cat's stellate ganglion starts at an impulse frequency of about two per second and slows markedly before ceasing With increased duration of preganglionic stimulation, the initial frequency remains relatively unchanged, but the discharge is much prolonged, sometimes lasting 30 seconds The highest frequency observed approached the highest attainable by perfusion with acetylcholine, much higher frequencies result from increased potassium or lack of calcium

Afterdischarge recorded from large bundles of postganglionic axons show that the various cells discharge with independent rhythms During this activity a single preganglionic stimulus evokes a response followed by temporary cessation of afterdischarge for one-fifth to one-half second

In perfused ganglia, the time course of after discharge is the same during perfusion as when stimulation is applied one minute after stopping perfusion. Thus afterdischarge is not caused by persistence of any chemical normally removed by the circulation.

Physiological standards C D LEAKE *Univ of Texas Medical Branch, Galveston* Trite is the custom to refer to physiological standards as "normals." This suggests presumptuous connotation of what ought to be. Such standards are merely averages or means of various observations on different presumably healthy organisms. To refer to such averages as "normals" causes semantic and practical confusion. Physiological averages or means are scientifically descriptive. We are in no position as yet to attempt to agree on what physiological standards ought to be. Such an attempt, involving possible purposes, may be an ethical proposition, for which scientific descriptive data is necessary, but merely as one factor to be considered. Physiological standards may be established by appropriately scientific, descriptive methods. The normative approach to such standards is not yet appropriate. Reference to physiological standards in normative terms is not yet justified.

The influence of testosterone propionate on the plasma proteins of hypothyroid rats JAMES H LEATHEM *Dept of Zoology and Bureau of Biological Research, Rutgers Univ, New Brunswick, N J* A decrease in thyroid activity is invariably followed by a rise in plasma globulin. When thiourea is used to induce the hypothyroid state a decrease in body weight and a reduction in food intake is observed but neither appears to be responsible for the rise in globulin concentration. Since testosterone propionate is known to cause urinary N_2 retention and since the seminal vesicle weights of adult rats on thiourea are subnormal a study of the effect of the androgen in normal and hypothyroid rats was undertaken.

Adult male rats were fed a stock diet plus 0.5% thiourea ad lib and 3 other groups were pair fed with this group. The latter received thiourea and testosterone propionate or were normal rats with and without the androgen. The experiments extended over 20-25 days and the daily dose of testosterone propionate (Perandren, Ciba) was either 0.1 mg or 0.5 mg. Rats receiving thiourea lost weight in excess of that lost by pair fed normal rats. Testosterone did not prevent the body weight loss. Total plasma protein levels and plasma globulin concentrations increased when thiourea was fed whereas plasma albumin decreased slightly but the latter change could be correlated with food intake. Testosterone did not decrease the plasma globulin level in the hypothyroid rat nor improve the plasma albumin concentration in hypothyroid or normal rats.

Hyperpneic tetany in commercial aircraft passengers LUDWIG G LEDERER and GEORGE J KIDERA (by invitation) *From the Medical Depts of Pennsylvania-Central Airlines and United Air Lines* Mild alkalosis, as the result of increased pulmonary ventilation, has been known to cause tetany. The reduction in the fares of air travel by means of commercial transport planes has opened a new market to unseasoned "first riders." In the course of a yearly study of passenger comfort, our attention was called to the occurrence in three individuals, all women, of tetanic-like seizures with true carpopedal spasm. In all instances, fear and anxiety preceded and accompanied a period of pulmonary hyperventilation. The onset in all three instances was gradual and identical with carpal numbness and spasm slightly preceding pedal numbness and spasm. As spasm developed, fear increased and hyperventilation was augmented. Instructions were issued to cabin personnel to have such individuals voluntarily induce apnea. In the event that the individual was uncooperative, rebreathing was suggested.

The incidence of tetany in air passengers from hyperventilation is not great. On the basis that the airline of one of us (LGL) now carries approximately 70,000 passengers per month, the incidence is practically nil and is reported merely because of its scientific interest and information.

A central action of adrenalin in raising blood sugar R LEIMDORFER, R ARANA and M HACK (all introduced by W S McCulloch) *Dept of Psychiatry and of Neurology and Neurosurgery, Illinois Neuropsychiatric Inst, Univ of Illinois College of Medicine* In cats under Dial, amytal, or unanesthetized, the effects of intracisternal injection of adrenalin on blood sugar were essentially similar. Under Dial, even 450 micrograms per kg of adrenalin intracisternally fail to affect blood pressure, whereas 5 micrograms per kg intraperitoneally usually produced a rise in blood pressure. Under amytal, 5 micrograms per kg intraperitoneally did not affect blood sugar. This concentration intracisternally raised blood sugar 30 mg per 100 ml and larger doses produced greater rises. Intravenous injection of 0.5 ml of cisternal fluid withdrawn two or more hours after intracisternal injection of about 40 micrograms per kg elevated blood pressure markedly with accompanying change in EKG and sometimes in respiration. Since the cat's volume of cerebrospinal fluid exceeds 2 ml and the observed response was comparable to that produced by 10 micrograms per kg, most of the adrenalin presumably remained in the cerebrospinal fluid. If it had passed into the blood it should have raised blood pressure as well as blood sugar. Hence, the action of intracisternal injection of adrenalin in raising blood sugar implies action on structures bathed by cerebrospinal fluid.

agents upon the postconvulsive (electric shock) EEG M A LENNOX (by invitation), T C RUCH, and B GUTERMAN (by invitation) *The Dept of Psychiatry and Lab of Physiology, Yale Univ School of Medicine* Immediate and prolonged EEG changes were observed after electric shock convulsions (shocking electrodes on the left temple and mid-occiput) in eighteen humans and ten monkeys. After the convulsion, the EEG became flat for one to three minutes. Then rolling 2-3 per second waves appeared most prominently in the frontal leads. Typically these lasted ten minutes after the first shock, and were then mixed with and replaced by 6 per second and finally by normal frequencies. The duration of the slowing increased after successive shocks and in humans invariably lasted days to weeks after five to ten shocks had been given. It is probably significant that in the only case in which occipital to occipital electric shocks were used, neither EEG slowing nor confusion lasted more than a few hours even after a series of twenty shocks. Slowing tends to be less marked in the monkey than in man. In monkeys the slow waves were also demonstrated by the technique of ventricular electroencephalography.

Six of ten monkeys reacted consistently and positively to benzedrine administered intramuscularly before the shock. In susceptible monkeys benzedrine repeatedly prevented the appearance of the 2-3 per second waves and the animals were clearly more responsive. Carbon dioxide was also effective but other drugs having vascular or central actions, adrenalin, amyl nitrite, aminophyllin, caffeine, prostigmine and nembutal in limited testing had no definite effect. Gynergen before benzedrine accentuated the slowing one animal. It is therefore uncertain whether the effect of benzedrine is due to its neural or vascular action [*Aided by the Knight Funds, Yale Univ School of Medicine*].

The mechanism of the fall in arterial pressure produced by high spinal anesthesia in patients with essential hypertension, W C LEVIN (by invitation) Griff T Ross (by invitation), RAYMOND ECHOLS (by invitation) and RAYMOND GREGORY *The School of Medicine, Univ of Texas*. The problem has been investigated by the continuous and simultaneous recording of the arterial and venous pressures before and during high spinal anesthesia in twelve studies on ten patients in whom a clinical diagnosis of essential hypertension had been made.

The data show no uniformity regarding the changes in arterial and venous pressures. The venous pressure may fall without any fall in the arterial pressure. The arterial pressure may fall greatly for a number of minutes before the venous pressure falls. The venous pressure may rise to control levels while the arterial pressure remains at the lowest level of fall caused by the spinal anesthesia.

patients with essential hypertension produces no uniform change in the relationship between arterial and venous pressures, that the changes in the arterial and venous pressures are not causally related, and that the fall in arterial pressure probably is not due to a diminished cardiac output produced by decreased venous return.

The influence of sugar and other metabolites on the respiratory exchange of eviscerated normal and depancreatized dogs, R LEVINE, CLARENCE COHN (by invitation), and SAMUEL SOSKIN, *Dept of Metabolic and Endocrine Research, Research Inst, Michael Reese Hospital, Chicago*. The utilization of glucose by liverless normal and diabetic dogs varies directly with the height of the blood sugar level. The utilized sugar may be partly transformed into fat or other metabolites. We endeavored to ascertain whether the fate of the disappearing carbohydrate could be followed more closely by a simultaneous determination of the respiratory exchange.

The oxygen consumption of liverless dogs is about 40 to 50 per cent lower than that of intact animals. It remains constant for at least 6 hours and is not influenced at all by the administration of glucose, pyruvate, fumarate or succinate. Glucose administration increases the production of CO_2 in both normal and diabetic animals, although higher blood sugar levels are needed for that purpose in diabetic dogs than in the normal group. There is no correlation between the amount of sugar utilized and the sugar equivalents of oxygen consumed or the CO_2 produced at any blood sugar level. Insulin raises CO_2 production without affecting the oxygen consumption. Glucose in the complete absence of insulin has the same effect but higher blood sugar levels are needed than in the presence of the hormone to produce equal results.

Of the substances tested only thyroxine will increase the respiratory exchange of eviscerated dogs.

Potentiating and pressor action of some n-substituted hexylamines JOHN R LEWIS (introduced by A M Lands) *Dept of Pharmacological Research, Frederick Stearns and Co, Division of Sterling Drug Inc, Detroit, Michigan*. A series of N-substituted hexylamines were studied for their effect on blood pressure and on potentiation of the pressor response of several sympathomimetic compounds. This series has the general formula, $\text{R}-(\text{CH}_2)_n-\text{NH}-\text{C}_6\text{H}_{13}$. It is divided into three groups: 1) $\text{R} = \text{CH}_3$ and $n = 0, 3, 4, 5, 6$ or $7, 2)$ $\text{R} = \text{phenyl}$ and $n = 1, 2, 3, 4, 5$ or 6 and $3)$ $\text{R} = \text{cyclohexyl}$ and $n = 0, 1, 2, 3, 4, 5$ or 6 . N-Methylhexylamine has the greatest pressor action, Di-hexylamine is next most active in the aliphatic series. N-(gamma-Cyclohexylpropyl)-hexylamine is about $\frac{1}{2}$ as active as the corresponding N-methyl derivative and has the greatest action of those com-

pounds containing a ring. In general, compounds containing a cyclohexyl ring are more active than those with a phenyl ring. Many compounds in this series potentiate the pressure response of epinephrine, β phenylethylamine, N-methyl β cyclohexylethylamine, ephedrine and a few other sympathomimetic agents. Inasmuch as ephedrine is also potentiated, the amine oxidase theory is not applicable to this series of compounds. The sensitivity of the effector cell may be altered or the action of other enzyme systems may be involved in the potentiation.

Acute toxicity was determined by intraperitoneal injection into albino mice. The approximate LD₅₀, in mg/kg, are: hexyl-zeta cyclohexylamine 15, N-hexylamine 25, hexyl-zeta-phenylhexylamine 25, dihexylamine 30, hexylcyclohexylmethylamine 50 and hexylbenzylamine 70. It should be noted that compounds containing a cyclohexyl ring are more toxic than those containing a phenyl ring. The toxicity increases when the length of the aliphatic chain between the ring and the nitrogen is increased. Dihexylamine is no more toxic than n-hexylamine.

Method of assaying adrenal preparations for protective action against toxic material (typhoid vaccine). LENA A. LEWIS (by invitation) and IRVING H. PAGE. *From the Research Division of the Cleveland Clinic Foundation, Cleveland, Ohio.* Protection by adrenal extract against toxicity of typhoid vaccine in adrenalectomized rats was reported by Hartman and Scott and the ineffectiveness of desoxycorticosterone acetate by Ettelson. With those observations as a basis, an assay for the protective effect of adrenal preparations against toxic material was developed. Rats are given saline drinking water following adrenalectomy and 5 days allowed to intervene. The minimal lethal dose of thyroid combined vaccine (Lederle) given intraperitoneally is then determined. Adrenal extracts are injected for three days. After the third morning injection 1.33 MLD typhoid vaccine is administered and percentage of survivals 24 hours later recorded. One toxic protection unit is the amount required per 24 hours to protect 90 per cent of adrenalectomized rats against 1.33 MLD typhoid vaccine.

Six adrenal extracts assayed 1.0, 10.0, 2.5, 2.2, 10.0 and 1.0 toxic protection units per ml. Fatigue tests ran parallel in all but one, namely 1.0, 10.0, 2.8, 5.0, 11.5 and 1.0 units respectively, one unit equalling the activity of 0.2 mg 11-dehydro-17-hydroxy corticosterone. Five mg desoxycorticosterone acetate exhibited less than one toxic protection unit.

While toxic protection activity parallels closely "carbohydrate activity", normal blood glucose levels do not in themselves protect for rats in

typhoid vaccine administration, succumb despite normal levels.

Assays for toxic protection activity are being made on additional extracts and crystalline materials. The usefulness of materials with high potency (toxic protection activity) in combatting shock of bacterial toxin origin is being studied. [Extracts were supplied by Dr M. H. Kuizenga, Upjohn Company and fatigue assays were done in their laboratories.]

The effect of methionine on the growth of protein-deficient rats exposed to benzene. TSAN-WEN LI (by invitation) and SMITH FREEMAN. *Dept of Physiology, Northwestern Univ. Medical School, Chicago.* Four groups of 6-9 male albino rats, weighing about 180 grams each, were fed a protein-deficient diet (sugar 69 per cent, casein 9 per cent, lard 15 per cent, salt mixture 4 per cent, cellophane 3 per cent, with 500 mg yeast and 2 drops of cod liver oil daily). The diet of two groups was supplemented with 0.8 per cent methionine making the sulphur intake equal to that provided by 30 per cent casein. One group on the basic diet and one on the supplemented diet were exposed to 600 PPM of benzene (90 per cent C_6H_6) for 42 hours weekly.

All the groups lost weight when placed on the low-protein diet but grew at varying subnormal rates thereafter, except that the exposed basic diet group continued to lose weight for two weeks and was still below its initial weight after six weeks. Both the methionine groups gained significantly more weight than their corresponding basic groups by the end of the sixth week. The difference between two exposed groups was nearly the same as that of the unexposed groups.

Both the exposed groups manifested leucopenia but the decrease in leucocytes occurred earlier in the group on the basic diet.

These results show that methionine can significantly increase the growth rate of rats on a low-protein diet. As compared to the effect of adequate protein, these results indicate that sulphur may not be the only factor in protein that influences the susceptibility of protein deficient rats to benzene. [Indebted to Velsicol Corporation for a grant and to Wyeth Inc. for methionine.]

The effect of inhaled methyl disulphide on benzene poisoning in dogs. TSAN-WEN LI (by invitation) and SMITH FREEMAN. *Dept of Physiology, Northwestern Univ. Medical School, Chicago.* (Read by title.) Eight adult dogs were exposed to a mixture of 600 PPM of benzene (90 per cent C_6H_6) and 6 PPM of methyl disulphide in an exposure chamber for 42 hours every week. They were fed high fat (33 per cent) low-protein diet which supplied 40 Calories and 0.8 gram casein per pound body weight daily as in experiments previously reported (*Am. J. Physiol.* 145: 166, 1953). The next

lessen the manifestation of benzene poisoning as it occurred in the protein-deficient dogs. On the contrary, impairment of Rose Bengal dye clearance was markedly depressed in some animals. Anorexia was also more pronounced in dogs receiving methyl disulphide as well as benzene. 6 PPM methyl disulphide has an adverse effect on protein deficient dogs exposed to 600 PPM of benzene. [This work was aided by a grant from the Velsicol Corporation.]

The effect of inhaled methyl disulphide on liver fat of rats. TSAN-WEN LI (by invitation) and SMITH FREEMAN, Dept of Physiology, Northwestern Univ Medical School, Chicago (Read by title). Twenty male albino rats weighing about 100 grams were divided into two groups. Using a paired feeding technique, they were fed a fatty liver producing diet (glucose 3 per cent, casein 15 per cent, cellophane 3 per cent, salt mixture 5 per cent, lard 40 per cent, with 500 mg yeast and 2 drops of cod liver oil daily). One group was exposed to a mixture of 600 PPM of heptane and 6 PPM of methyl disulphide 42 hours weekly for 21 days. The liver fat of the exposed group was 20.5 ± 5.6 per cent and that of the unexposed group was 23.8 ± 7.3 per cent. The difference was not statistically significant.

Another twenty rats were fed the same diet with one group exposed to heptane without methyl disulphide. The liver fat of the exposed group was 22.4 ± 7.5 per cent and the control group was 18.7 ± 6.2 per cent. The difference was not statistically significant.

These results fail to show any lipotropic effect from the concentration of methyl disulphide used in this experiment. 600 PPM of heptane did not significantly influence rats maintained on high fat-low protein diet. [This work was aided by a grant from the Velsicol Corporation.]

The relationship of alveolar and arterial oxygen tensions. J. L. LILIENTHAL, JR., and R. L. RILEY (by invitation), School of Aviation Medicine, U. S. Naval Air Station, Pensacola, Fla. (Read by title). The difference between alveolar pO_2 and arterial pO_2 results from two factors: A) the pressure gradient from alveolus across "pulmonary membrane" to intra-cellular hemoglobin, and B) the admixture of blood which has not passed through adequately ventilated alveoli (including venous contributions to arterial blood). Modern views hold that A is small (ca. 1 mm Hg), there is little evidence from which to estimate the size of B.

The alveolar-arterial (a-a) pO_2 difference has been measured in men at rest and exercising, at sea level and during anoxia (tracheal $pO_2 = 75$ mm) by new methods. The average a-a differences during rest were 9 mm (air) and 9 mm (anoxia). During exercise a-a differences were 18 mm (air) and 15 mm (anoxia).

With reasonable assumptions for A-V oxygen differences, theoretical considerations make it possible to calculate the relative contributions of A and B to the observed a-a pO_2 differences. These calculations indicate that when breathing air the membrane gradient (A) is 1 mm, and that venous dilution (B) lowers arterial pO_2 ca. 8 mm. During anoxia, however, a venous dilution of similar proportions will produce only negligible effects on arterial pO_2 (< 1 mm), and the remainder of the a-a difference during anoxia must arise from membrane gradient. Furthermore, the 8-fold increase in membrane gradient which this implies is necessary theoretically to accomplish the observed rate of oxygen transfer across the pulmonary membrane under anoxic conditions (Barcroft, *Lessons from high altitudes*, 1925). [The opinions or assertions contained herein are the private ones of the writers and are not to be construed as official or reflecting the views of the Navy Dept. or the naval service at large.]

Studies on the mixing of gases within the respiratory system with a new type nitrogen meter. J. C. LUNT, (introduced by D. W. Bronk), E. R. Johnson Foundation, Univ. of Pennsylvania. In studying respiratory processes, the analysis of the role of the gas mixing which occurs in the respiratory passages has been hampered by a lack of experimental methods which can record fast changes in gas composition. In the present study, rapid physical methods were used to record gas volumes (an electrical condenser manometer) and gas concentrations (a nitrogen meter, which photo-electrically records the ultraviolet light emitted by this gas as it flows through a continuously evacuated electrical-discharge tube).

The subject breathes oxygen until the expired gas contains less than 1% nitrogen. While holding an inspiration, he is connected to the recording devices and an air mixture. The record is started on the first expiration and continues during subsequent respiratory cycles. The expiration following the first inhalation of air produces a record which is divided into three nitrogen fraction phases: 1) 70 to 125 cc of air diluted with water vapor, 2) 100 to 150 cc of gas with rapidly falling N_2 fraction, 3) the remaining expired volume at an effectively constant N_2 concentration. Phases 1 and 2 are tentatively named "the kinetic deadspace", for an inert gas. Phase 3 gives essentially the same N_2 fraction at the end of both normal and maximal expirations. Phases 1 and 2 are relatively independent of ventilation velocities, and have approximately the same volumes in normal respiration, hyperventilation, and in vital capacity maneuvers. From these records, the kinetic dead space, residual volume, total instantaneous lung volume and maximal lung volume, have been calculated, and were satisfactorily reproducible. [Work

done under contract with the Office of Scientific Research and Development]

Analysis of lactic acid with a modification of the Conway microdiffusion unit ALFRED G. LISI and WILLIAM M. HART (introduced by J. Earl Thomas) *Depts. of Pharmacology and Physiology, Jefferson Medical College, Philadelphia, Pa.* A modification of the Conway microdiffusion unit was developed to permit analyses of smaller quantities of lactic acid than heretofore possible with this simple apparatus. Analysis of lithium lactate and various tissues were performed where the quantities of lactic acid determined ranged from 1.1 μ g to 18.0 μ g. In contrast to the standard glass unit which is about 68 mm in diameter, the unit employed in this work is only 25 mm in diameter. It is machined from a solid, clear, plastic rod one inch in diameter.

The procedure is based on the work of Winnick (*J. Biol. Chem.* 142, 451, 1942) although certain changes were found necessary in this work. The lactic acid is oxidized to acetaldehyde by ceric sulfate in the outer chamber of the unit. The acetaldehyde, by simple diffusion, is absorbed by sodium bisulfite in the inner chamber. The familiar Clausen iodometric titration is then carried out, performing the final titration with a Landerstrom-Lang and Holter mercury screw micro burette. [Aided by a grant from the Markle Foundation.]

Diuresis resulting from intravenous infusion of urine J. MAXWELL LITTLE, J. E. HAWKINS, JR., and HAROLD D. GREENE *Dept. of Physiology and Pharmacology, The Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C.* In experiments designed for another purpose, (Green, Little and Hawkins, *Fed. Proc.* 1946), the intravenous infusion of urine into catheterized dogs anesthetized with morphine-pentobarbital usually resulted in a marked diuresis. After the control urine flow was determined, the urine collected at 15 minute intervals from the recipient animal and from 1 or 2 donor dogs was infused into the recipient animal at 15-45 intervals.

The average control urine flow in 22 recipient dogs was 2.9 ml/15 min (range 0.9-7.2). The flow accelerated immediately in 4 experiments, within 30 minutes in 8, and within 4 hours in 9 (average 5.8 minutes). Within 15 minutes the volume excreted equalled the volume infused in 4 experiments, within 1 hour in 5 experiments, and within 4½ hours in 11 experiments. In 1 experiment the volume excreted never equalled that infused and in 1 experiment the urine flow did not exceed the control rate. Since the donor and recipient urines were combined, the volume infused progressively increased reaching maxima of 6.7-53.8 ml/15 min (average 25.2). The maximal urine flows were 3.3-57.3 ml/15 (average 21.7). The total period of infusion ranged from 3 to 7 hours. Each infusion of urine, regardless

of its size, was followed by an abrupt but temporary depression of mean arterial pressure.

In 4 experiments continuous infusion of physiological saline at average rates of 6.4 ml/15 min, for an average of 4.3 hrs, was accompanied by average urine flows of 3.5 ml/15 min. Similar results were reported with small single infusions of physiological saline (Little et al, *Am. Jour. Physiol.* 142, 246, 1944).

Use of the immature guinea-pig for estrogen assay JAE L. LITTELL (by invitation), JOHN TOM (by invitation) and CARL G. HARTMAN *Dept. of Zoology and Physiology, University of Illinois, Urbana* (Read by title). As in rats and mice the guinea pig vagina opens for the first time with the onset of the first estrus. In the guinea-pig the vagina remains open only during estrus (2 to 4 days), the closure membrane being intact in the dioestrus, throughout pregnancy and in ovariectomized females.

From 1 to 5 days after careful subcutaneous injection of estrogen in oil, or of woman's blood (obtained from finger), into the lateral lips of the vulva, the closure membrane opens, closing again after 2 or 3 days in the adult and after 7 to 10 days in weanlings. The dosage of blood, or of estrogen in oil, is given in two injections, one on each side of the closure membrane, the needle being directed medially. The guinea-pig has proved to be as sensitive as the 16-day rat (cf. Hartman and Littell, *Science*, August 17, 1945), responding to as little as 0.02 cc of female blood and to 0.000,01 milligrams of estrogen in oil. Castrated or immature females seem best adapted to quantitative assay.

An automatic device for continuous frequency analysis of electroencephalograms HANS LOWENBACH and IAN BARBOUR (introduced by F. D. McCrea) *Depts. of Physiology and Neuropsychiatry, Duke Univ. Hospital and School of Medicine, Durham, N. C.* The interpretation of human electroencephalograms is currently based upon the recognition of more or less marked deviations from a relatively regular, rhythmically repetitive pattern which is assumed to be "normal" because it is found in a great number of individuals who are subjectively and objectively healthy. The predominant amplitude and the predominant frequency are described only in general terms, such as high, low, fast, slow, etc.

It is desirable to reduce complex electroencephalographic curves to the constituent Fourier frequencies. The procedure of Gibbs and Grass (1938) is too complicated for routine use, and moreover only small, arbitrarily selected, sections of the record are analyzed. The usefulness of the apparatus of Grey Walter (1943) is limited by its mechanical nature, it is slow, non linear, and does not produce a continuous curve.

In this paper an apparatus will be described which analyzes electroencephalograms (or other bio-electrical phenomena) electrically, automatically, continuously, and simultaneously with the standard procedure of recording. The basic principle is similar to that of a heterodyne radio. A vibrating bar serves as the tuned filter element because of the low frequencies involved. The oscillator frequency is controlled by a condenser that varies synchronously with the passage of the recording paper, on which the output is recorded by an ink-writing Grass oscillograph. A number of analyses of electroencephalograms of normal individuals and of persons suffering from different cerebral disorders will be presented as examples.

Determination of renal function in rats B E LOWENSTEIN (by invitation) A C CORCORAN and IRVINE H PAGE *Research Division of the Cleveland Clinic Foundation, Cleveland, Ohio*. Modern methods of renal functional study have been applied in rats by the following method: females weighing 100 grams or more are lightly anesthetized and a metal urethral catheter (20 G) inserted into the bladder. A mixture of mannitol and p-aminohippurate or of mannitol and diodrast in saline is injected in divided intraperitoneal and subcutaneous doses. At the end of 25 minutes blood is sampled, the bladder irrigated with 1 or 2 cc of saline and the mixture of urine and washings discarded. Thirty minutes later the bladder is washed and the mixture of urine and washings kept as the urine sample. Blood is again sampled. The mean of the concentrations of mannitol, p-aminohippurate or diodrast in the two plasma samples is taken as the representative concentration during the clearance period. Mannitol, p-aminohippurate or diodrast clearances and the tubular secretory capacities (Tm) of the latter substances are calculated.

Mannitol clearance of the rat, taken as equal to glomerular filtration rate, is thus found to be about 0.0067 cc per gm body weight per minute and Tm_{PAH} to be about 0.0015 mg p-aminohippurate per gm per minute. Tm_{diodrast} approximates 0.0027 mg diodrast-iodine per gm per minute. Thus the ratio Tm_{PAH}/Tm_D in the rat is about 0.6 in contrast to the ratios of about 1.7 which were obtained in man and dog. The disparity of Tm ratios in the rat as compared to human beings and dogs suggests that the mechanism of diodrast and p-aminohippurate secretion are not, as had been thought, identical.

Studies on the cause of pain in high altitude "bends" D W LUND and J H LAWRENCE (introduced by Laurence Irving) *Univ of California, Berkeley, California*. During exposure of human subjects to simulated altitudes of over 34,000 feet in a decompression chamber, subjects who developed severe "bends" in areas suitable for massage or "milking," e.g., in the elbows, knees, and

ankled, were lowered to, and maintained at, an altitude at which the pain was materially decreased or absent. A firm massaging or milking stroke was then applied by an investigator. The stroke was started in the mid-portion of the limb and carried centrally or peripherally toward the initially indicated area of pain. In all successful instances the massaging hand was stopped short of the initial point of pain.

In twenty instances of massage among 15 subjects pain was reinduced or increased at the lower altitude in 11 instances. In four other instances the shift of pain closer to the joint ahead of the massaging hand was noted. In one instance of these four, a rolling tourniquet was accompanied by the movement of the pain from a point just below the patella, ahead of the tourniquet to the ankle. Release of the tourniquet was followed by return of pain to the original site at the knee. (This phenomena has been observed in two additional instances not recorded in this series). In five attempts no increase or return of pain and no change of the location of pain was noted.

It is concluded that these observations support the concept that "bends" pain may be caused by collections of gas in the fascial and inter-muscular septal planes, which by dissecting to the periosteal insertions of such anatomical layers, cause pain at these insertion points. [*The work described in this abstract was done under contract with the Office of Scientific Research and Development*]

Effect of anoxic anoxia on stomach emptying time of rats fed corn oil P L MACLACHLAN *Dept of Biochemistry, School of Medicine, West Virginia Univ, Morgantown* (Introduced by E J Van Liere) (Read by title). There is considerable evidence that anoxic anoxia results in a diminished motility and a prolongation of the emptying time of the stomach, in both man and dogs. Studies on the effect of anoxia on fat absorption have shown that the amount of fat absorbed by rats subjected to partial pressures of oxygen of 63 mm and 53 mm Hg was significantly less than for corresponding controls. That this observation could not be explained on the basis of a prolonged emptying time of the stomach, however, has been shown by the administration of corn oil (1.385 gm) to previously fasted adult albino rats and subjecting them to a partial pressure of oxygen of 53 mm Hg (approximate altitude, 28,000 ft) for 2, 3 and 4 hour periods. An equal number of simultaneously fed control animals were kept at atmospheric pressure. The amount of fat remaining in the stomachs of the anoxic rats 2 hours and 3 hours after feeding was significantly less than for the corresponding controls. On the other hand, no difference was found at the end of 4 hours. These findings indicate an initial acceleration of the emptying of the stomach of rats

as a result of exposure to diminished oxygen tension

The phosphatase activity of human spermatozoa
JOHN MACLEOD and WILLIAM H SUMMERSON (by invitation) *Depts of Physiology and Anatomy and Dept of Biochemistry Cornell Univ Medical College, New York, N Y* The phosphatase activity of human spermatozoa has been determined manometrically and chemically in the presence of certain phosphate esters which are of known significance in the carbohydrate metabolism of other tissues The substrates used were ATP, ADP, adenylic acid, the various hexose mono- and diphosphates, β glycerophosphate and acetyl phosphate Because of the powerful and heterogeneous phosphatase activity of human seminal fluid, the results presented are based on the activity of spermatozoa washed several times to eliminate as much of the seminal fluid as possible

In the presence of ATP, the spermatozoa showed a phosphate splitting power equivalent to two-thirds of the total phosphorous of ATP This would correspond to the formation of adenylic acid from ATP Similarly, in the case of acetyl phosphate, the spermatozoa show a powerful phosphate-splitting activity

The spermatozoa did not show any phosphate-splitting activity in the presence of any of the other phosphate esters studied though the seminal fluid and *once* washed spermatozoa did produce considerable hydrolysis of *all* of them Whether this is due to the inability of these substrates to penetrate the cell structure is not known

The relation of these observations to the motile activity of the spermatozoa has also been studied

A slide rule for pH of indicators and buffers and for bicarbonate equilibria J F McCLENDON *Research Lab of Physiol, Hahnemann Medical College, Phila* (Read by title) By substituting log

$\frac{\alpha}{1-\alpha}$ for the A scale (of an ordinary slide rule) and

marking the midpoint (pK index" and substituting an L scale for the B scale the following calculations may be made 1) When the pK index is set over the value of pK of an indicator (B scale), under the fraction of the indicator showing the alkaline color (A scale) will be found the pH (B scale) 2) When the pK index (A scale) is set on the pK_1 value of a buffer (B scale), under the fraction of buffer acid neutralized (A scale) will be found the pH 3) At 38° , subtract pH of blood or bicarbonate solution from pK_2 (7.62) and place this difference on the B scale over the left hand 1 on the D scale Under the millimols of fixed base on the C scale will be found the pressure of CO_2 in mm Hg on the D scale

Concentric zones of distribution of fluorine in milk and dental caries J F McCLENDON and WM C FOSTER (by invitation) *Research Lab of*

Physiol, Hahnemann Medical College, Phila Mills divided the U S into zones of frequency of dental caries in children by parallels of latitude and we found a correlation coefficient between his data and our determinations of fluorine in milk of -0.37 The data for caries (and defective teeth) in draftees of World War I are much more extensive and the low point coincides with the high point of fluorine in milk (Deaf Smith County, Texas) Around this center lie Texas, New Mexico, Arizona, Colorado, Nebraska, Kansas, Missouri, Arkansas and Oklahoma with 3-7 rejectees due to dental caries per 1000 draftees, and 34, 26, 21, 14, 12 and 10 parts of fluorine per 10 million of dry milk The rest of the U S forms an outer zone with 7-48 rejectees per 1000 and 7, 8, 9, 10, 11 and 12 parts of fluorine per 10 million of dry milk

The effect of d-tubocurarine on the electrical activity of dogs' brains A R MCINTYRE, A L DUNN (by invitation), and P E TULLAR (by invitation) *Dept of Physiology and Pharmacology, Univ of Nebraska College of Medicine, Omaha* In dogs, lightly anaesthetized with various barbituric acid derivatives, the electrical activity of the brain may be modified by the intravenous injection of d-tubocurarine The first effect is transient and consists of greatly increased activity, occipital, parietal, and frontal regions are affected almost simultaneously, and the voltage may increase threefold The frequency is irregular and sometimes exhibits spikes followed by a burst of high frequency (100 C P S) low voltage volleys Immediately following the transient changes described, the electrical activity is depressed, the depression may occur with doses insufficient to prevent diaphragmatic respiration With larger doses the electrical activity of the frontal areas is decreased very rapidly and the initial stimulation may be very brief The depression of the frontal areas occurs before peripheral paralysis It is interesting to note that the conclusion reached by Brodie in 1812 "that woorara acts on the brain" is thus confirmed These observations provide pharmacological evidence for the use of curare as an adjuvant in anaesthesia [This work was aided in part by a grant from E R Squibb and Sons]

Studies on the chronic toxicity of DDT in the dog BERNARD P MCNAMARA¹ (by invitation), RICHARD J BING,² and FRANCES HOPKINS (by invitation) *Pharmacology Section, Medical Division, Chemical Warfare Service, Edgewood Arsenal, Md* The ingestion of 100 mg/kg of DDT over periods varying from 2 weeks to 5 months initiated coarse tremors which disappeared upon withdrawal of the drug The daily administration of larger doses (150 to 250 mg/kg) for the same period of time resulted in severe neurological symptoms, consisting of

¹1st Lt, Sn-C, A US

²Capt MC A US

tremor, exaggeration of the stretch reflex and the placing reaction, and aberrations in gait (overstepping). Withdrawal of the drug after several weeks resulted in a cessation of tremors while other neurological symptoms persisted for one or two days. In doses exceeding 250 mg/kg, DDT produced persistent neurological symptoms after less than 3 weeks of administration. Tremors, positive supporting reaction, hyperextension and exaggeration of altitudinal reflexes persisted as long as 6 days after cessation of such dosage. Cerebellar dysfunction, as suggested by the neurological symptoms, has been confirmed by the pathological study of Haymaker & Ginzler, of the Institute of Pathology, U S Army Medical Museum.

The prolonged administration of DDT (150 to 300 mg/kg daily) produced a fall in hemoglobin without significant reduction in red cell count.

Daily administration of DDT (150 to 300 mg/kg) produced an increase in cardiac output and systolic discharge associated with a decline in arterio-venous oxygen difference. The oxygen consumption showed no change from control values. DDT failed to elicit any change in the glomerular filtration rate and effective renal plasma flow. However, there was produced a slight degree of early impairment of liver function, which became terminally more severe in some animals.

Human tolerance to centrifugal force repeated hourly throughout a day. C A MAASKEL, *Physiological Branch, Aero Medical Lab, Engineering Division, Air Technical Service Command, Wright Field, Ohio*. Following repeated exposures to high radial accelerations, either in a human testing centrifuge or in aircraft, some personnel may complain of varying degrees of fatigue (subjective). To determine whether such repeated physiologic stresses had any effect upon the individuals G-tolerance per se, 8 young men, who had a known G-tolerance history of many months, were given complete G-tolerance assays at intervals of 45 minutes to an hour throughout the normal working day on the Air Technical Service Command human testing centrifuge. This series of assays also served as a control in a benzedrine medication study.

The standard AAF technique was used to determine the highest acceleration tolerated with retention of clear vision in a ten second interval. Likewise the lowest accelerations which produced dimming, narrowing and complete loss of vision (blackout), and in some cases loss of consciousness were determined in ten second exposures.

Complete abolition of vision was lost at 4.8 Gs with a range from 3.6 to 7.2. There was no significant difference in any of the values for the various symptom levels either individually or collectively throughout the series of repeated hourly exposures for an entire day.

Comparative toxicity of penicillin for animals and plants. DAVID I MACHT *Dept of Pharmacology, Laby of Sinai Hospital, Baltimore*. A dozen different makes of penicillin were examined. Toxicity for animals was tested on white mice by intraperitoneal and subcutaneous injection. Doses of Penicillin ranging from 500 to 15,000 Oxford units per cubic centimeter produced no toxic effect whatever. Doses of 20,000 units per cc produced some depression, the M L D was in the neighborhood of 25,000 units per cc for mice weighing 25 grams. Toxicity for plants was tested on seedlings of *Lupinus albus*, measuring the elongation growth of their roots in plant physiological solutions at 60° F in the dark, for 24 hours by the author's well known phytopharmacological method. Penicillin is very much more toxic for plant protoplasm than for animals. Solutions of 200 Oxford units per cc gave only 40% of normal growth, those of 5 units per cc only 60% of normal growth, those of 1 unit per cc 75%, and those of 0.5 unit, gave a growth index of 85%. Even weaker concentrations of penicillin produced a definite inhibition in growth when studied by especially delicate plant physiological methods. An extensive study is in progress to build up a curve of growth by means of which it may be possible to determine at least approximately the amount of penicillin present in samples of blood.

Comparison of opiates, demerol, and cobra venom on cats' pupils. DAVID I MACHT *Dept of Pharmacology, Laby, Sinai Hospital, Baltimore* (Read by title). Unanesthetized cats were given injections either hypodermically or intraperitoneally. Morphine sulphate 1 to 5 mg produced maximum mydriasis and very great excitement of the animals. Similar maximal dilatation and agitation were produced by dilaudid 0.025 to 0.05 grain. Pantopon 4 to 8 mg gave maximal mydriasis but less excitement. Injections of codein and papaverin produced no significant change in the size of the pupils. Demerol 10 to 20 mg caused maximal mydriasis and great excitement undistinguishable from that produced by morphine. Cobra venom 5 to 10 mouse units was followed by no change or by slight myosis of the pupils and produced a sedative instead of exciting effect on the behavior of the cats. Cocain hydrochloride injections 4 to 20 mg produced marked dilatation of the pupils and tremor. Injections of benzedrine sulphate made the cats wild and produced maximal dilatation of the pupils. The duration of maximal mydriasis was longest after morphine and demerol.

Influence of snake venoms on prothrombin time of normal and hemophilic blood. DAVID I MACHT *Dept of Pharmacology, Labys of Sinai Hospital, Baltimore* (Read by title). Prothrombin time was measured on plasma samples of cats, normal man, and 2 hemophiliacs by employing solutions of vari-

ous snake venoms 1 10,000 to 1 200,000 in physiological saline, and comparing the results with prothrombin time determined by Quick's thromboplastin method. The venoms examined were those of *Naja tripudians*, *Naja nivea*, *Naja Bungarus*, *Burmese Cobra*, *Bungarus fasciatus*, *Daboia* (or *Russell's Viper*), *Bothrops atrox* (or *Fer de Lance*), *Ankistrodon mocassen*, *Hemachatus hemachatus*, *Bothrops jararaca*, *Bitis arietans*, and several species of *Crotalus* or rattlesnakes. In optical concentrations, the cobra venoms produced coagulation in 3½ to 8 minutes, *Bungarus fasciatus* (Krait) in 4 to 6 minutes, *Bothrops atrox* in 5 to 6 minutes, *Ankistrodon mocassen* in 3 to 4 minutes, *Crotalus* venoms in 6 to 8 minutes, *Hemachatus (Ringhals)* and *Bitis* in 1 to 2 hours. The most rapidly acting venoms were found to be those of *Daboia* (Russell's Viper) and of *Bothrops jararaca*, they produce complete coagulation in 15 to 30 seconds. There is very little difference in prothrombin time between normal and hemophilic blood irrespective of whether Quick's thromboplastin or snake venoms are used for the test.

Pharmacodynamic reactions of previously irradiated organisms DAVID I. MACHT *Depts of Pharmacology and Radiology, Sinai Hospital, Baltimore* (Read by title). The growing importance of radiology as regards biological effects prompted an inquiry into drug action on previously irradiated animals and plants. Zoopharmacological experiments were made on mice exposed to doses of 63 r to 210 r from Roentgen tubes operated on 200 K V, 50 ma, and at 50 cm, filtered through 2 mm copper. Some drugs produced the same effect on irradiated as on normal animals, others were more toxic for X-rayed mice, while still others were less toxic for irradiated animals. Sulphadiazine, a chemotherapeutic agent, had the same potency for both sets of mice, digitalis, a heart drug and cobra venom, a medullary poison, were more toxic for X-rayed than for normal mice, while HgCl₂, the kidney poison, is actually less poisonous for previously irradiated than for normal ones. Mice injected with HgCl₂ first, and then radiated within two hours, survived in 40% to 50% while control mortality was 90-100%.

Phytopharmacological experiments were made on *Lupinus albus*. Here again some drugs acted exactly the same on normal and X-rayed plants. Other drugs were more toxic for irradiated plants while still others were less toxic for seedlings previously treated with X-rays. Sulphadiazine and para amino benzoic acid produced exactly the same effects on radiated as on normal seedlings. Digitalis and atabrine were less toxic for growth of X-rayed plants. Epinephrine was equally toxic for both. Ephedrine, penicillin, and snake venoms became more toxic for the X-rayed plants than for controls.

The irradiations were made through courtesy of Dr. Marcus Ostro, Chief of the Radiological Department of Sinai Hospital.

Thromboplastic properties of mercurial diuretics DAVID I. MACHT *Dept of Pharmacology, Labys of Sinai Hospital, Baltimore* (Read by title). Following the author's discovery of the thromboplastic action of digitalis and other digitaloids (*Annals Int Med*, XVIII, 772, 1943), an investigation was begun of certain mercurial diuretics. These are known to have produced sudden death, at the height of their clinical administration. Nearly 200 experiments were made on rabbits and cats, blood for coagulation tests by Howell's method being drawn either directly from the heart or from the carotid artery. The drugs studied were two mersalyl derivatives, namely, mercupurin and salyrgan (without theophylline), and mercuhydrin. These were found to produce marked shortening of coagulation time noted for 3 and more hours after both intravenous and intramuscular injections. An analysis of the thromboplastic dynamics revealed no significant changes in platelet counts or blood calcium, but there was a definite diminution in prothrombin time, and in antiprothrombin, and a decrease in fibrinogen produced by the drugs. Several other organic mercury compounds and even bichloride of mercury also exerted definite thromboplastic effects.

Experimental detoxification of pemphigus blood DAVID I. MACHT and MARCUS OSTRO (by invitation) *Depts of Pharmacology and Radiology, Sinai Hospital, Baltimore* (Read by title). The Macht-Pels phytotoxic reaction of pemphigus blood serum (*Proc Soc Exp Biol and Med* 1927, XXV, 237, *Arch Dermat and Syph* 1929, XIX, 640, 1931, XXIII, 601, 1934, XXIX, 206) has been applied up to the present writing to over 2500 blood specimens, and proved to be accurate diagnostically in over 90% of patients. The present authors, being engaged in studying the effects of X-rays on blood, found that pemphigus sera exposed to suitable rays *in vitro* were completely detoxified by 63 r to 105 r of Roentgen energy, as judged by phytopharmacological tests on *Lupinus albus* seedlings, by Macht's method (*Jour Lab and Clin Med* 1941, XXVI, 597). The most effective rays in this respect are those passed through a composite filter of 2 mm Cu at 200 K V, 50 M A, and 50 mm target distance. Two severe clinical cases of Pemphigus with very toxic blood, when radiated with 105 r over the spleen, yielded a completely detoxified blood serum, as tested phytopharmacologically for several days after treatment.

The effects of blood pressure changes, reflexly induced, on glomerular activity and renal plasma flow in the unanesthetized rabbit J. P. MAES and R. P. FORSTER (by invitation) *Dept of Physio-*

logical Sciences, Dartmouth Medical School, and Dept of Zoology, Dartmouth College Creatinine clearance and para aminohippuric acid clearance were determined in unanesthetized rabbits, as described in another report (F & M, this meeting) Under local anesthesia the depressor nerves were severed and changes induced in the blood pressure (determined from the femoral artery) by clamping and releasing the carotid arteries

Of all animals studied 11 were chosen for this report because the control values were especially suitable for analysis

In 7 animals the kidneys had been denervated and the adrenals demedullated several weeks before the experiment Occlusion of the carotid arteries in these animals, while raising the blood pressure, would presumably not cause reflex renal vasoconstriction nor liberation of adrenaline In six cases an increase in creatinine clearance (glomerular filtration rate) followed each rise in blood pressure The para-aminohippuric acid clearance (effective renal plasma flow) increased with the pressure in 4 cases The amount of glucose reabsorbed per minute usually increased with the creatinine clearance This is interpreted as indicating an increase in the number of active glomeruli

In a second group of 7 animals the kidneys and the adrenals were normal The results in this group were not as homogeneous as in the former However, in some cases the para-aminohippuric acid and creatinine clearance increased with the blood pressure

Righting activity in spinal and decerebrate cats after d-amphetamine H M MALING (by invitation) and G H ACHESON *Dept of Pharmacology, Harvard Medical School, Boston, Mass* Postural behavior suggestive of righting activity was observed in acutely spinal or decerebrate cats after the intraperitoneal injection of d-amphetamine, usually in a dose of 10 mg per kg

The decerebrate cat lying on its side would slowly lift its head from the table and turn it so that its eyes were almost level Meanwhile the forelegs would take a position tending to right the shoulders Similar but less marked righting activity occurred in the rump, accompanied by elevation of the tail slightly above the table

This activity was accentuated by contact of the cat's side with the table after a period of support in the air, by stimulation of the toes or of the perineal region, or by acceleration of the animal upward or downward while in mid-air in side position Especially with acceleration, the tail underwent rotary motions, as seen in the righting of intact animals

Of 20 cats with complete sections of the spinal cord at levels between C6 and T8, 11 showed the same rotary motions of the tail when laid on the side and when the lateral aspect of the hind knee which next to the table was rubbed Eight others lifted

their tails from the table during this rubbing Ten of the 20 cats responded to this rubbing with incomplete righting of the rump, accomplished by movements of the hindlegs and elevation of the lumbar spines from the table

D amphetamine appears to activate righting mechanisms present but usually inapparent in acutely spinal or decerebrate cats

Electrocardiographic changes in hemorrhagic and ischemic compression shock JOSEF MANNIQUE (introduced by Carl J Wiggers) *Dept of Physiology, School of Medicine, Western Reserve Univ, Cleveland, Ohio* Dogs received morphine and sodium barbital anesthesia Electrocardiographic leads were the three standards, four or five precordials and three augmented unipolars Arterial blood pressure was measured continually In seven dogs electrocardiograms were taken before hemorrhage, during hemorrhagic hypotension with blood pressure of 50 and 30 mm Hg, after reinfusion and during irreversible shock

In another group of nine dogs both hind legs were wrapped from ankle to groin with rubber tubing which was released after six hours, resulting in shock Electrocardiograms were taken before and after release of the tubing

Results Hemorrhagic shock Changes seen after hemorrhage were displacement of S-T segment with partial or complete recovery following reinfusion of blood There was also a tendency for the T wave to become increased in amplitude and sharper in contour, simultaneously with the above changes

Ischemic compression shock Changes seen were displacement of S-T segment before release of tubing,—usually with partial recovery after release In one case, after release, the QRS complex was changed in shape and amplitude

After release of the tubing in four dogs, the hind legs were massaged, with the following results in different dogs S-T segment displacement, auricular fibrillation, and ventricular fibrillation Other changes, after massage, not electrocardiographic, were a markedly decreased beat rate, pulsus alternans, decreased blood pressure, blood pressure waves resembling irregular Traube-Hering waves, and decreased survival time

The effect of air movement on human response to heat and humidity JOHN P MARBARGER (by invitation) and CRAIG L TAYLOR, *Aero Medical Lab, Air Technical Service Command, Wright Field, Dayton, Ohio* The effect of air movement on tolerance for heat and humidity during short periods of exposure (60 minutes) was studied on the nude, sitting subject General details of experimental plan, test environments and methods of analyzing the data in this series are similar to those described in another abstract, (C L Taylor and J P Marbarger) Two subjects previously tested in "still air," (0.5 miles per hour) were exposed to

air movements of approximately 3, 5 and 10 miles per hour, in each environment, except the extreme hot dry conditions which proved to be intolerable for 60 minutes exposure with wind. The air movement, produced with a large blower, evenly ventilated the front body surface from head to foot. Air speed was measured throughout the experiments with a heated glove anemometer.

The physiological index of heat strain (numerical combination of heart rate, skin and rectal temperatures) increased directly with air movement in the hot dry environment, reflecting increased convective heat gain since the air temperature was above skin temperature. In the hot-humid environment, however, air movement decreased the index at moderate vapor pressures but increased it at extreme vapor pressures. Relative to this index, sweat loss was higher in the hot-dry and lower in the hot-humid, thus confirming a similar effect found in the "still air" environment experiments.

The delimitation of separately innervated regions of single skeletal muscles.¹ J. E. MARKEE and H. LÖWENBACH (by invitation) *Dept. of Anatomy and Depts. of Physiology and Neuropsychiatry, Duke Univ. School of Medicine, Durham, North Carolina*. In certain long muscles of the limb of the dog segmental contraction can be induced by stimulation of the separate nerve branches entering the muscle. Segmental contraction can also be induced by stimulation of successive nerve roots. A morphological study in the human demonstrated that nerve branching occurs in a similar way, but this finding throws no light on the distribution of the nerve fibers within the muscle. In the dog, we recorded the segmental participation of the limb muscles photographically but because the "segmentation" of the muscle was necessarily arbitrary, this study, too, does not reflect the true state of affairs.

To delineate biologically, in the dog, the boundaries of the segments, we stimulated successively the nerve branches entering a muscle and mapped out the corresponding regions from which an action current could be obtained.² It appears that the areas of innervation are quite distinct with relatively little overlapping. The areas of innervation do not conform to any known structural boundaries. For example, in the *m. rectus femoris* the three areas that can be excited separately are of triangular shape, the proximal and distal areas nearly meeting on the medial side of the muscle. The configuration of separately excitable regions recorded in a number of limb muscles will be illustrated by lantern slides.

Anticonvulsant effect of pregnenolone M

¹ Aided by a grant from the National Foundation for Infantile Paralysis Inc.

² The technical assistance of Mr. Ian Barbour is gratefully acknowledged.

MARKS (by invitation), H. T. WYCIS (by invitation) and E. A. SPIEGEL *Dept. of Exp. Neurology, Temple Univ. Medical School, Philadelphia, Pa.* Former studies from this laboratory (Spiegel, *Fed. Proc.* 2: 47, 1943; Spiegel and Wycis, *Fed. Proc.* 4: 67, 1945) revealed an anticonvulsant effect of some steroids, among them acetoxypregnenolone. It seemed therefore of interest to extend these studies to pregnenolone.¹ In female as well as male rats, the threshold for electrically induced convulsions was raised to 1.7-3 times the normal value on intraperitoneal injection of pregnenolone (20-25 mg per kilogram body weight dissolved in propylene glycol, 4-5 mg per cc). On intramuscular injection, larger doses were necessary to obtain an anticonvulsant effect. 30-40 mg intraperitoneally produced ataxia. In cats and dogs (male and female), the threshold was raised to 1.6—over 3.0 times the premedication value with intraperitoneal injections of 30 mg pregnenolone per kilogram body weight (1% solution in propylene glycol). In some animals, an increase in threshold could be observed for several days after a single injection. The anticonvulsant dose did not change the general behavior of the animals. With 40 mg per kilogram, the dogs and cats were slightly ataxic. Still larger doses (50 mg per kilogram) produced in them a picture resembling more or less catalepsy, spontaneous movements being reduced, correction of abnormal postures being retarded with preserved ability to walk on stimulation and to react to pain. In contradistinction to bulbocapnin catalepsy, an increase of muscular tonus was not noticeable.

Respiratory water loss at ground level and altitude. LOUISE H. MARSHALL (introduced by Heinz Specht) *National Inst. of Health, Bethesda, Maryland*. Water vapor in the exhaled air of human subjects was condensed and frozen out in a chilled brass canister and weighed to a precision of 0.3%. Respiratory volumes and rates were determined during collection of the water vapor. Resistance to respiration was kept to a minimum, and care taken to ensure complete drying of mask and tubing before and after use.

Determinations were made at ground level with the subjects breathing dry oxygen at room temperature and performing moderate exercise. The average lung water loss at ground level was approximately 300 mg per minute, or nearly 32 mg per liter (STP dry) exhaled gas. This corresponds to complete saturation at 31°C, or 70% saturation at normal body temperature.

At a simulated altitude of 30,000 feet, other conditions remaining the same, approximately 10% less water per minute was exhaled. The minute volume at altitude decreased to a greater extent. This resulted in a slightly higher water vapor con-

¹ Kindly supplied by Dr. E. Henderson and Dr. E. Schwenk, Schering Corporation.

tent per liter exhaled gas at 30,000 feet than at ground level

Spinal and peripheral synaptic susceptibility to nembutal (sodium pentobarbital) as shown by vesicular responses A W MARTIN, HELEN M KIPPLE (by invitation), J M DILLR (by invitation) and BERNICE G HARRIS (by invitation) *Dept of Animal Biology and Dept of Pharmacology, Univ of Washington, Seattle* Contractions of the urinary bladder, produced by electrical stimulation of the central end of the pudendal nerve in the spinal rabbit, were abolished by intravenous administration of 10-20 mg /kg of nembutal

Stimulation of preganglionic fibers of the pelvic nerve causes contraction of the bladder Intravenous injection of 20-40 mg /kg were required to inhibit this response 80 per cent Increase to 80-100 mg /kg produced little further inhibition This appeared to be due to the presence of some post-ganglionic fibers at this locus of stimulation, an explanation which was borne out by the fact that nicotine produced nearly the same degree of inhibition to electrical stimulation of this nerve Therefore 20-40 mg /kg may be considered to produce complete inhibition of the synapse between pre- and post-ganglionic neurones

Perfusion of the bladder with defibrinated blood appeared essential to the successful study of the post-ganglionic endings Doses of 10-20 mg per 100 cc of blood (roughly 100-200 mg /kg) produced reversible inhibition of the visceral neuro-myal junction in 15 to 20 minutes That this was not an effect upon the smooth muscle fibers was shown by the persistence of their response to direct application of acetyl-choline solution to the surface of the bladder To prevent this muscle response to acetyl-choline a quantity of about 100 mg per 100 cc of blood (roughly 1 gm /kg) had to be used This inhibition too was reversible

Effects of proteins on the resistance to anesthesia produced by barbiturates GEORGE MASSON *Dept of Anatomy, McGill Univ, Montreal, Canada* Rats treated with crude extracts of beef anterior pituitary are more sensitive to nembutal anesthesia This increased sensitivity appears after the first few days of treatment, is maintained during the entire treatment and, furthermore, subsists after its cessation Since nembutal was the only anesthetic used, we decided to test various barbiturates Male rats weighing 80-100 g were injected subcutaneously with pituitary preparations (40 mg a day of lyophilized glands) for a period of 6 days On the 7th day each barbiturate was administered intraperitoneally, according to body weight A group of controls received the same dose of barbiturate The following conclusion can be drawn the sensitivity to barbiturates detoxified mainly in the kidney, is not modified by pituitary extracts, while the sensitivity to barbiturates de-

toxified in the liver is increased (pentothal excepted) The degree of this increase in sensitivity is inversely proportional to the duration of action of the anesthetic In order to investigate the specificity of the pituitary extracts, rats were injected with various extracts of beef tissues and various proteins at the daily dose of 40 mg All tissue extracts were active Among the proteins, casein, Ca caseinate, egg albumen and zein increased the duration of nembutal anesthesia, while gelatin, amigen and serum were devoid of activity Since non specific damaging agents (cold, formalin, exercise) are inactive, it seems that the increased sensitivity is mostly related to the proteins contained in the pituitary extracts and not due to any hormonal factor It is suggested that the assimilation of foreign proteins interferes with some important mechanism necessary for the detoxification of barbiturates [Aided by a grant from the John and Mary R Markle Foundation]

The use of carbon dioxide in preventing post-exercise orthostatic circulatory insufficiency H S MAYLORSON *Dept of Physiology, School of Medicine, Tulane Univ* In a previous publication (*J Aviat Med*, 15 301, 1944) it was shown that many individuals faint when kept motionless in the upright position after performing a standard amount of moderate exercise Their post-exercise response is particularly characterized by a low and rapidly falling systolic pressure and circulatory failure within five to ten minutes after the exercise is finished In the present study, ten such "fainters" have been made to breathe air containing from 4 to 7 p c CO₂ for varying intervals after the exercise When CO₂ is given immediately after, the post-exercise systolic pressure level is high and drops only gradually, syncope does not occur and the pattern of responses resembles that of the "non-fainter" Likewise, the administration of CO₂ when syncope is imminent results in a reversal of the pattern of response and averts the collapse

Respiratory gas analyses indicate that the CO₂ content of alveolar air in "fainters" is diminished after the exercise and remains from 25 to 40 p c lower than the pre-exercise level whereas the drop in "non-fainters" is less (5 to 25 p c) Venous and arterial blood gas analyses are in progress It is tentatively suggested that, under the conditions of our experiments, the level of CO₂ in certain individuals ("fainters") falls below that necessary to stimulate the vasomotor center and that the rise in the systolic pressure following the administration of CO₂ is due to stimulation of the center and a consequent vasoconstriction which counteracts the local dilatation produced during the exercise

The experimental production of static tremor FRED A METTLER *Dept of Neurology, College of Physicians and Surgeons, Columbia Univ, New*

York. The commonplace, so called "resting" tremor of the neurologic clinic is an experimental rarity. It is well known that experimental efforts, based on current theories of the pathology of paralysis agitans have invariably failed to elicit static tremor. Available knowledge of the neuropathology of this disease is, however, of notably poor quality. It remains to be seen what information may be obtained by pathological inquiry directed toward the cerebellar apparatus.

Static tremor has been accidentally encountered in one case of lesion of the brachium conjunctivum (Ferraro and Barrera), in an unspecified number of short-lived cases of diffuse lesion in the region of the brachium (Walker and Botterell) and in ten cases of damage of the cerebellar apparatus (Mettler).

In the latter cases tremulous movements were highly variable in quality and persistence. The most pronounced and durable examples occurred in association with brachial interference. Subsequent work has tended to confirm the hypothesis that reasonably persistent static tremor depends upon a pathologic complex in which interference with the cerebellar apparatus is a necessary factor. The modulating effects of other lesions are under investigation.

In none of our experimental cases did we feel justified in describing the resultant tremor as one of strict rest. There is also a large body of clinical opinion which prefers to speak of Parkinsonian tremor as static rather than resting (Benda and Cobb) and as present under greatly variable conditions of background activity (Hoefler and Putnam) [Aided by the Wm J Matheson Commission].

The urinary excretion of thiamine, pyramin (the pyrimidine-like component of thiamine) and riboflavin by man in semi-starvation. OLAF MICKELSEN (introduced by Ancel Keys) *Laby of Physiological Hygiene, Univ of Minnesota, Minneapolis, Minnesota*. Three-day urine samples were collected from 34 subjects at the 12 and 24 week periods of semi starvation (cf. Keys, *Fed Proc*, 1946). They were analyzed for thiamine by the thiochrome procedure, for pyramin by the yeast fermentation method and for riboflavin by the fluorometric technique. The diet during this period provided 1.29 mg thiamine and 0.71 mg riboflavin per day. At the 12 and 24 week periods, the excretions were in mg per day with the standard deviations: thiamine 0.121 (± 0.060) and 0.132 (± 0.071), pyramin 0.135 (0.018) and 0.132 (± 0.027)—and riboflavin 0.056 (± 0.035) and 0.056 (± 0.030). The largest contributor of thiamine in the diet was whole wheat bread which was varied in amount from subject to subject in order to maintain his desired rate of weight loss. The thiamin excretion showed a -0.56 and a $+0.70$ correlation to the bread intake at the 12 and 24 week periods, the

correlation of the pyramin excretion and bread intake at these periods was $+0.416$ and $+0.813$. The pyramin excretion showed a $+0.514$ and a $+0.300$ correlation to the B.M.R. respectively, a -0.24 and a $+0.66$ correlation to the thiamin excretion at the 12 and 24 week periods. The riboflavin excretions are among the lowest we have ever seen, in some cases, the daily excretion was 0.014 mg. The correlation between the riboflavin excretion of each man at the 12 and 24 week periods was $+0.549$. [This work was supported in part under a contract with the Office of Scientific Research and Development. Support from other sources will be acknowledged in final publication.]

Analysis of the normal T-1824 disappearance curve. A. T. MILLER, JR. *Dept of Physiology, Univ of North Carolina School of Medicine, Chapel Hill*. Despite widespread use of the dye method for determining plasma volume, there is lack of agreement on fundamental issues concerning interpretation of the disappearance curve. Some of these issues were reinvestigated on normal, unanesthetized dogs, with the following results.

(1) The best approximation to linearity is obtained by plotting logarithm of dye concentration against time. Deviation from linearity occurs in the square root of time plot.

(2) The slope of the disappearance curve is steep, and varies in different animals, during the first hour, less steep and more constant during the next 24 hours (rate of dye loss = 6 to 8 per cent per hour).

(3) The form of the curve is constant for a given animal for many months.

(4) Mixing of the dye in the bloodstream is complete in 5 to 33 minutes. Mixing time is independent of the amount of dye injected between the limits of 0.5 and 5.0 mg per kg of body weight.

(5) Mixing time is reduced or abolished by a previous injection of dye or of India ink. Our data oppose the view of Cruickshank and Whitfield (*J Physiol* 103: 19P, 1944) that the mixing curve is due to rapid removal of dye by reticulo-endothelial cells. The significance of the mixing curve is being investigated.

(6) Variability in duration and slope of the mixing curve makes calculation of plasma volume from single samples open to question. Fair approximation to true initial dye concentration is obtained by multiplying the dye concentration of a 10 minute sample by 1.04.

Dog hemoglobin parenterally well utilized to maintain weight and nitrogen balance. Utilization improved by DL methionine but not by DL isoleucine. LEON L. MILLER (introduced by G. H. Whipple) *Dept of Pathology, School of Medicine and Dentistry, Univ of Rochester*. Dog hemoglobin (laked red blood cells) given intraperitoneally as virtually the sole source of nitrogen intake in normal dogs main-

tains approximate urinary nitrogen balance with slight weight loss. Hemoglobin is less effective in this respect than parenteral plasma proteins.

When supplemented with dl-isoleucine dog hemoglobin given intraperitoneally is no better utilized and slight weight loss persists.

Dl-methionine supplementation on the contrary, results in positive nitrogen balance and maintenance or slight gain of weight. The further addition of dl-isoleucine does not improve the effect of methionine.

The contribution to protein economy of hemoglobin liberated during normal red cell obsolescence and break down is not insignificant.

The above experiments demonstrating maintenance of the adult dog by parenteral plasma or hemoglobin are at variance with reports showing failure of rats to grow when fed human or beef globin unless supplemented with isoleucine.

Speed of response of arterial oxygen saturation to rapid change in equivalent altitude. G. A. MILLIKAN, E. R. Johnson Foundation, Univ of Pennsylvania. A sudden change in the equivalent altitude (or in the gas composition of the inspired air) produces a corresponding change in the oxygen content of arterial blood whose extent and time course depend upon the depth and frequency of respiration, the functional residual lung volume, the efficiency of mixing in the lungs, and the cardiac output. These relations are being studied by simultaneous registration of respiration (Pappenheimer-Lilly flow meter) and blood saturation (oximeter) using instruments whose time resolving power is a small fraction of one respiratory cycle.

When pure oxygen replaces a low-oxygen breathing mixture, there is a time lag in the resting subject of about 7 seconds before the saturation starts abruptly to rise. This delay is reduced in exercise to about 3 seconds, reflecting the increased rate of blood flow from the lung to the ear. Subsequent changes in the saturation can be compared with that predicted from the respiratory pattern. [Work done under contract with the Office of Scientific Research and Development.]

Breath-holding time in anxiety states. I. ARTHUR MIRSKY, E. LIPMAN (by invitation) and ROY R. GRINKER (by invitation). May Inst for Medical Research, Cincinnati, Ohio, Michael Reese Hospital, Chicago, Illinois. Young male patients suffering from a variety of anxiety states were tested as to their breath-holding capacities under various tensions of alveolar CO₂. The latter was produced by different degrees of alveolar ventilation before holding the breath.

Essentially, the test consisted in measuring the length of time that a subject could hold his breath, (a) under ordinary respiration, (b) after a single extra deep respiration, and, (c) after six extra respirations. The timing was started at the end of

inspiration. It was noted that decreasing the alveolar CO₂ resulted in an increase in the subject's capacity to hold his breath. Thus, in a group of normal subjects a single extra respiration induced a 91% increase in the average breath-holding time, while six extra respirations induced an increase of 155%. Since the subjects were not aware of the effect of hyperventilation, motivation could be excluded as a factor in the breath-holding time.

It was observed that the average breath-holding time in a group of twenty-two men was 45 seconds after no extra ventilation, 86 seconds after a single extra ventilation, and 111 seconds after six extra ventilations. A group of sixty-two patients with anxiety states, when subjected to the same procedures, had an average breath-holding time of 28 seconds, 55 seconds and 67 seconds, respectively. Statistical analysis revealed the reliability of the difference between the two groups of men to be over six, which suggests that the difference between the normal and abnormal patients is of clinical significance.

Heat exchanges of man in cold outdoor environments. G. W. MOLNAR (by invitation) and E. F. ADORIN. Dept of Physiology School of Medicine and Dentistry, Univ of Rochester, Rochester, N. Y. Men in shorts were exposed to outdoor environments for 1 to 4 hours in sitting, lying or standing positions. As position showed no significant effect, all results were averaged. In the shade, heat production was augmented at air temperatures below 18°C at a rate of about 10 Cal/hr for each Centigrade degree fall in temperature. In the sunshine, heat production increased only when air temperature was below 10°C.

Surface temperature, averaged for ten points, dropped 0.6° per Centigrade degree decrease in air temperature in the shade. In the sunshine the temperature was higher. After the first hour, surface temperature remained nearly constant. Assuming that the stored heat lost during the first hour can be estimated from changes in surface and rectal temperatures, the man in the shade cooled about 15 Cal/hr per Centigrade degree air temperature below about 30°C. In the sunshine, the rate was the same, but cooling occurred only at air temperature below 25°C. This estimated stored heat loss was greater than heat production during the first hour, the rate of total sensible heat loss was, therefore, twice that of heat production, and amounted to about 650 Cal/hr at 1°C air temperature. The threshold for stimulating heat production could be body cooling of about 200 Cal during the first hour. Turning on the sun is equivalent to raising air temperature about 5°C, or man gains about 65 Cal/hr from the autumn sun. [Work done under contract with the Office of Scientific Research and Development.]

Vitamin A levels of dog plasma. (Read by title.)

W G Moss (introduced by G E Wakerlin) *Dept of Physiology, Univ of Illinois College of Medicine, Chicago* Seven dogs were found to have plasma levels of vitamin A in the same range previously reported for humans (42-187 Gamma per 100 cc) However the carotene values were always negative in contrast to human plasma which contains 70-290 Gamma per 100 cc Plasma tolerance curves on eleven dogs using 25,000 and 50,000 I U of vitamin A were similar to those reported for humans (300,000 I U) except that the dog plasma levels returned more slowly to normal During the administration to twelve dogs of 200,000-400,000 I U per day for six months, the fasting plasma levels usually ranged from 500 to 2,000 Gamma per 100 cc and in some dogs exceeded 5,000 Gamma per 100 cc The plasma levels remained well above normal even two years after vitamin A was discontinued

Vitamin K and experimental renal hypertension (Read by title) W G Moss (by invitation) and G E WAKERLIN *Department of Physiology, University of Illinois College of Medicine, Chicago* We previously reported a study of the possible anti-hypertensive effect of several vitamins in experimental renal hypertension (Fed Proc, 3 34, 1944) More recently we assayed the possible anti-hypertensive activity of vitamin K in six dogs One animal received vitamin K in sesame oil (Menadione) in a dose of 30-60 mg daily by mouth for 3 months Four dogs were given vitamin K powder (Kappaxin) mixed with food in a daily dose of 60 mg for six months The sixth dog received the latter dose intramuscularly in sesame oil for six months None of these animals showed any significant change in their hypertension

Our findings with vitamin K are at variance with those reported by Oppenheimer et al (J Mt Sinai Hosp, 11 23, 1944) and Schwartz and Ziegler (Proc Soc Exp Biol and Med, 55 160, 1944) for hypertensive rats Certainly our results do not warrant trial of this vitamin in the treatment of human hypertension as suggested by the latter [Aided by grants from the John and Mary R Markle Foundation and the Graduate School Research Fund of the University of Illinois]

On the rôle of acetylcholine during nerve activity D NACHMANSOHN *From the Dept of Neurology, Columbia Univ, College of Physicians and Surgeons, New York, N Y* Based on a new approach a new concept has been developed as to the rôle of acetylcholine during nerve activity This approach is based on the study of the enzymic mechanisms involved and their correlation with events in the living cell recorded by physical methods The results obtained indicate that the release of acetylcholine is an intracellular process directly associated with the nerve action potential

Three essential features of the enzyme studies are (1) the high potential rate of acetylcholine

metabolism in nerves indicated by the concentration of cholinesterase, (2) the exclusive localization of cholinesterase at the neuronal surfaces where the bioelectric phenomena occur and (3) the specificity of the enzyme in all nerve tissue whether central or peripheral, afferent or efferent, vertebrate or invertebrate

Acetylcholine has been associated with the action potential in three ways (1) a direct correlation between voltage of the action potential and cholinesterase activity has been established on the electric organ The line correlating the physical and chemical event passes through the 0 point indicating a genuine relationship, (2) adenosine triphosphate, the primary source of chemical energy released during nerve activity, is used for the synthesis of acetylcholine This is consistent with the idea that release and removal of acetylcholine are responsible for the primary alterations of the nerve membrane during the passage of the impulse (3) anticholinesterasic compounds abolish reversibly the action potential of the axon This supports the assumption that acetylcholine acts by depolarizing the membrane and that if its removal by cholinesterase is inhibited, a state of depolarization persists

A gradient of gastro-intestinal motility following hemorrhage H NECHELES, L WALKER (by invitation) and WAR OLSON (by invitation) *Dept of Gastro-Intestinal Research, Research Inst of Michael Reese Hospital, Chicago, Ill* Gastro-intestinal motility was recorded in unanesthetized dogs with chronic fistulas and in dogs anesthetized with pentobarbital sodium, morphine barbiturate, or ether After a control period, varying amounts of blood were withdrawn Following small hemorrhages, which did not affect blood pressure materially, or following larger hemorrhages, which lowered blood pressure considerably, as well as during the period in which blood pressure fell gradually towards zero, the following observations were made Motility of the colon increased in most experiments, notwithstanding whether local or general anesthesia was used The motility of the stomach, of the gastric antrum and of the small intestines in most experiments either was not changed or was depressed, but there was stimulation of motility in a number of experiments, depending on the type of anesthesia employed

The response of the upper gastro intestinal tract, i.e. stomach and duodenum, showed a decrease of motility in most experiments, the middle part of the gastro intestinal tract, the ileum, showed little or no effect on motility, whereas in the lowest part of the tract, the colon, a persistent increase in motility was observed

It is believed that the stimulation of colonic motility by hemorrhage is not due to the drop of systemic blood pressure, but either to local vaso

constriction or to increased impulses from parasympathetic nerves

The effect of air movement on the loss of heat by evaporation, convection, and radiation from nude and clothed individuals N. NILSON¹ (by invitation), L. W. EICHNA² (by invitation), W. B. SHELLEY³ (by invitation), and S. M. HORVATH¹ *Armored Medical Research Laboratory, Fort Knox, Ky* (Read by title) Three acclimatized men were studied calorimetrically while standing (nude or clothed) or marching (clothed only) on a treadmill in a hot room wind tunnel. The effects of five wind velocities, ranging from 30 to 600 ft/min, were determined in each of seven hot environments in which the dry bulb air temperatures (wall temperature equal to air) varied from 90° to 120°F and the wet bulb temperatures from 69° to 91°F. Measurements included rectal, skin and clothing temperatures, oxygen consumption, evaporated and total sweat loss. Analysis of data on totally wetted nude men (at least 10% sweat evaporated) revealed that the relationship between air movement and evaporative heat loss from the totally wetted body could be described by the formula $E/\Delta P \pm 1.4V^{0.4}$ where E = evaporative heat loss, Cal/M²/Hr, ΔP = difference in vapor pressure of water at skin temperature and in room air, mm Hg, and V = wind velocity, ft per min. A tendency toward a similar relationship between evaporation and wind velocity was found with clothed subjects when the clothing was fully wetted. Heat transfer by convection and radiation, satisfactorily calculated only for the nude man in the 120°F environments, could be related to air flow in the following manner: $C + R/\Delta T \pm 5.6 + 0.53V^{0.5}$ where $C + R$ = convective and radiant heat transfer, Cal/M²/Hr, ΔT = temperature difference between air and skin, °C, and V = wind velocity, ft/min. The value 5.6 represents the heat exchange by radiation between the subject and walls. It agrees with values calculated in accordance with accepted physical principles.

Determinations of cardiac output in the dog by the ballistic method J. L. NICKERSON *Dept of Physiology College of Physicians and Surgeons, Columbia Univ* A critically-damped, ballistic system (J. L. Nickerson and H. J. Curtis, *Am J Physiol* 142: 1, 1944; J. L. Nickerson, *Fed Proc* 4: 202, 1945) has been constructed of a suitable size for work on the dog. The movements of the ballistic system are recorded by optical means.

The values of the cardiac output from the ballistic method were computed by equations of the form found satisfactory in the work on humans. Simultaneous determinations were also made with the Fick method employing right ventricular

catheterization. These studies were made on normal anesthetized dogs and on dogs in a variety of shock-like conditions involving large changes in cardiac output. Although the agreement between the Fick and the ballistic results from dog to dog is only fair, the agreement between the two methods when cardiac output changes in a single animal are observed is considerably more accurate. [Work done under contract with the Office of Scientific Research and Development.]

Intermittency of blood flow in peripheral fields PAUL A. NICOLL and R. L. WERN (by invitation) *Dept Physiol, Indiana Univ, Bloomington and Dept Anatomy, College of Medicine, Univ Ill, Chicago* Intermittency of blood flow through local areas have been reported frequently. The mechanism responsible, its mode of regulation and its functional significance are variously explained. Most workers now agree that the true capillaries play only passive roles and the flow patterns result from the activity of smooth muscle cells around the arterioles.

Study of intermittent flow in normal mammalian tissue, without the use of anesthesia or surgical procedures, is easily carried out in the expanded skin folds or wings of the bat (*M. lucifugus*). The arterioles have a single layer of circular type smooth muscle, each cell of which forms a tight spiral around the vessel. Contraction of any individual spiraled cell has a sphincteric action. On the terminal arterioles the space between the spiral cells increase and capillary branches usually possess only one such cell close to their origin. Here they form the so-called pre-capillary sphincters. It is the activity of these spiraled smooth muscle cells that determines flow patterns in the capillary beds.

The most frequent activity is a rhythmical alternation of constriction and relaxation along entire networks. However individual terminal arterioles and pre-capillary sphincters often exhibit complete independence in their cyclic behavior. The more peripherally along the system one studies the behavior of these spiraled cells, the more independent becomes their activity.

Anoxia, carbon dioxide and liver glycogen L. F. NIMS, L. L. LANGLEY (by invitation) and R. W. CLARKE *Laby of Physiology, Yale Univ School of Medicine, New Haven, Conn* Fasting rats, exposed to atmospheres simulating altitudes from 15,000 to 30,000 feet for a period of 24 hours, show a rise in liver glycogen from 0.5 per cent (controls) to a maximum of 3.6 per cent. Maximum accumulation of liver glycogen occurs at a simulated altitude of 20,000 feet, lesser accumulations at higher and lower altitudes. Accumulation of liver glycogen is related to time of exposure to the high altitude, increasing progressively from 6 to 24 hours. These results might be explained as an effect of anoxia *per se* on the adrenal-hepatic mechanism, or as an

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² Major, MC, AUS

³ Captain, MC, AUS

effect of the reduction of body carbon dioxide by the attendant hyperventilation. Addition of carbon dioxide to the rarefied atmospheres in amounts sufficient to yield partial pressures from 8 to 48 mm Hg reduced the effect of high altitude on the adrenal-hepatic mechanism. At partial pressures of carbon dioxide from 30 to 46 mm Hg, glycogen accumulation did not occur in significant amounts. It is concluded that the effect of simulated high altitude, in producing liver glycogen accumulation, is more nearly related to a loss of carbon dioxide, a result of anoxic hyperventilation, than to anoxia *per se*. [Work done under a contract with the Office of Scientific Research and Development.]

The effect of chloral hydrate on the gastric emptying time in man. DAVID W. NORTUP and EDWARD J. VAN LIERE. *Dept of Physiology, West Virginia University School of Medicine*. It was previously shown by us (*Journ Pharmacol and Exper Therap* 37: 142, 1941) that Sodium Amytal decreased the emptying time of the stomach. In the present study a different type of hypnotic, chloral hydrate, was administered just prior to the ingestion of a standard test meal containing BaSO₄. Emptying time was determined fluoroscopically. Twelve subjects were used, at least three control determinations and three determinations following chloral hydrate were made. A hastening of gastric emptying was observed in eleven of the twelve subjects, statistically significant in three cases. It is concluded that chloral hydrate in the dosage used (0.6 gm) has a slight but definite stimulating effect on gastric emptying.

The influence of wine on gastric acidity. ERIC OGDEN. *Univ of Texas, School of Medicine, Galveston, Texas*, and FRANK D. SOUTHARD, JR., (by invitation). *University of California Medical School*. Eight normal male students were studied while fasting and for 2½ to 3 hours after taking soda crackers and 200 ml of test fluid. The test fluids consisted of—distilled water, white table wine, 14% ethanol solution, dealcoholized wine, and a solution of cream of tartar adjusted to approximate the pH and titratable acidity of the wine. Free and total acidity were titrated on samples withdrawn at twenty-minute intervals, each test being repeated twice on each subject.

After wine, both curves rose higher, achieved their peak later, and were prolonged, as compared with water. After alcohol the curves resembled the wine curves in intensity and peak, but the acidities tended to rise and fall more rapidly than with wine, and an occasional extremely high acidity occurred.

The curves after acid or dealcoholized wine tended to rise little and to sustain the rise for a long time. In some individuals this rise began early, in others gastric secretion appeared to be completely repressed for an hour or more.

The effect of the acid or other effects recognizable

in the curves for dealcoholized wine may account for the less violent but more sustained stimulation of gastric secretion which wine gives in contrast to alcohol. [Acknowledgment is made for help from the Division of Fruits Products of the Univ of California College of Agriculture and from the Wine Advisory Board.]

Circulatory failure induced by partial cerebral ischemia. DAVID F. OPDYKE. *Dept of Physiology, Western Reserve Univ, Cleveland, Ohio*. Occlusion of the innominate and left subclavian arteries in the dog results in a partial cerebral ischemia which is accompanied by an initial increase in total peripheral resistance (TPR) and mean blood pressure but produces no symptoms of cerebral ischemia unless the central carotid pressure is reduced to 30 mm Hg, or less. In about half of the experiments TPR was maintained above the control level throughout the occlusion period. Thus offered an opportunity to determine whether a prolonged period of increased TPR with normal blood pressure would produce circulatory failure as claimed.

The cephalic arteries were occluded and the blood pressure rise prevented by hemorrhage (1-2 per cent of body weight) or by a blood pressure compensator. The arterial clamps were removed after 1-3 hours, all withdrawn blood reinfused and the subsequent course of events observed. The results fell into two groups. Some dogs exhibited a progressive circulatory failure beginning immediately after occlusion. These dogs failed to maintain the increased TPR and central carotid pressure was lower than in the following group. The second group maintained the increased TPR and essentially normal blood pressure throughout the occlusion period, but developed circulatory failure after release of the arterial clamps.

It is concluded on the basis of the latter experiments that a prolonged increase of TPR with blood pressure remaining normal will induce a subsequent circulatory failure which closely resembles that seen in hemorrhagic shock.

Performance as related to composition of alveolar air. A. OTIS (by invitation), H. RAHN, M. EPSTEIN (by invitation), and W. O. FENN. *Dept of Physiology, School of Medicine and Dentistry, Univ of Rochester, Rochester, New York*. In order to determine the separate and combined effects of anoxia and acapnia on performance and on heart rates, the Hecht Contrast Discrimination Test and a hand steadiness test were administered to individuals whose alveolar oxygen and carbon dioxide were maintained at various desired tensions in a high altitude chamber. The results are plotted on the pCO₂ pO₂ diagram, and regions of various kinds and degrees of performance are indicated. Acapnia and anoxia appear to be additive rather than antagonistic in their effects on test scores, and performance impairment may be analyzed into anoxic

rabbits, following the oral administration of 0.5 gm of pregnenolone, 1.5 mg of pregnandiol were isolated from the urine. Small amounts of pregnandiol were isolated from the bile and urine of a patient undergoing bile drainage following the oral administration of pregnenolone. No pregnenolone nor its metabolic products other than pregnandiol could be isolated in any of these experiments.

The metabolism of pregnenolone will be discussed in connection with the demonstrated biological conversion of progesterone to pregnandiol and of cholesterol to pregnandiol.

Reactions of the spinal cord to laminectomy. T. L. PEELE (by invitation), R. A. GROAT AND W. F. WINDLE *Dept of Anatomy, Duke Univ, Medical School and Inst of Neurology, Northwestern Univ Medical School, Chicago* (Read by title). Under nembutal, a 28-mm length of spinal cord was exposed under exacting aseptic precautions in cats for 0 to 60 minutes. Conditions varied as follows: normal heat and light and dura unsutured, dura sutured, dura unopened, exposure in dark, exposed cord immersed in warm Ringer's, tantalum plate closing bony defect. All animals showed functional disturbances 24-36 hours later. These were motor and sensory. Persistent spastic paraplegia occurred in some. Animals were sacrificed 1 to 60 days after operation. Connective tissue overgrowth occurred at exposed site after 7 days. Deformity of the cord was noted in all. Macroscopical areas of softening appeared in a few. Evidence of hemorrhage sufficient to account for physiological disturbances was found in no animal.

Histopathology was present in all specimens. In its mildest form the reaction consisted of perivascular lymphocytic infiltration and pavingmenting of the lymphocytes in small veins as early as 3 days. Further progression usually occurred, with graded pathology consisting of more intense infiltration, glial proliferation, transformation of lymphocytes into gutter cells, fiber degeneration, chromatolysis, softening and cavitation. Damage was predominantly secondary, since it was many times greater than the possible primary damage to cells or fibers occurring as a direct result of the disturbances to which the cord had been subjected. [Work done under contract, sponsored by CMR, between OSRD and Northwestern Univ.]

Further observations on effects of g forces. V. A. PERTZOFF (by invitation), S. W. BRITTON AND R. F. KLINE (by invitation) *Physiological Lab, Univ of Virginia Medical School, Charlottesville*. Determinations of blood pressure and blood flow on exposure to high accelerations have been made on monkeys, dogs and other animals. Both head and foot ends of animals (carotid, brachial, femoral arteries) were studied under various forces. Comparison of pressure changes was made with a hydro-

dynamic model on the centrifuge under similar experimental conditions.

The protective influence of various devices, injected materials, etc., was studied. Extended observations were also made on EEG changes under different conditions. [This work was done under a contract with the Office of Scientific Research and Development.]

The sensitization of the myocardium to sympathetic stimulation during acute DDT intoxication in animals. FREDERICK S. PHILIPS¹ (by invitation), AIFRED GILMAN,² AND FREDERICK CRISCITELLI (by invitation) *Pharmacology Section, Medical Division, Chemical Warfare Service, Edgewood Arsenal, Md*. Following the intravenous administration of lethal, convulsant doses of DDT (peanut oil solutions emulsified in isotonic saline containing lecithin) a small percentage of rabbits and cats and most dogs succumb as the result of ventricular fibrillation. In dogs death from ventricular fibrillation occurs during the first convulsive episode. Inasmuch as DDT is a chlorinated hydrocarbon, a type of compound which can sensitize the myocardium to epinephrine or sympathin and since sympathetic discharge is a prominent feature of DDT-induced convulsions, it became apparent that sudden death during acute intoxication might result from fibrillation of a sensitized heart subjected to excessive sympathetic stimulation.

Ventricular fibrillation was induced in 8 of 11 anesthetized dogs (phenobarbital) 30 to 60 minutes after the intravenous administration of 75 to 100 mg/kg of DDT by the intravenous injection of 0.01 (5), 0.015 (1), 0.02 (1), or 0.04 mg/kg (1) of epinephrine. Furthermore, in curarized monkeys and dogs, which had received 75 to 100 mg/kg of DDT intravenously, convulsive seizures, as evidenced by increased spontaneous electrical activity of the brain, initiated cardiac arrhythmias or ventricular fibrillation.

It is thus apparent that DDT not only sensitizes the myocardium in a manner similar to other chlorinated hydrocarbons but also as a result of its central convulsant action causes the sympathetic discharge necessary for inducing fibrillation.

Duration of renal ischemia required in dogs to produce damage of lethal degree.³ PHILLIPS, R. A.⁴ AND P. B. HAMILTON (by invitation) *U. S. Navy Research Unit at the Hospital of The Rockefeller Inst for Medical Research, New York*. The following procedure was applied with aseptic precautions under pentobarbital anesthesia to a series of female dogs. Through a mid-line abdominal incision the right kidney was excised. The left

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² Major, Sn C, A US

³ The Bureau of Medicine and Surgery does not necessarily undertake to endorse views or opinions which are expressed in this paper.

⁴ Commander (MC) USNR

kidney was mobilized by dividing between ties the parietal peritoneum and the accompanying capsular vessels about one inch from kidney. The renal artery was dissected free down to its origin from the aorta and its lumen was obliterated for varying periods of time with the aid of two serrefines. When renal ischemia was produced for more than 60 minutes the abdominal incision was closed with layered sutures during this period. Following the removal of the serrefines the abdominal incision was closed with layered silk sutures.

Of the 12 dogs subjected to renal ischemia for 1 or 2 hours all survived for over one month, of 6 dogs subjected to renal ischemia for 3 hours one died on the fourth post-operative day. This animal had an abscess containing over a liter of *B. coli* infected pus in the abdominal cavity. The remaining 5 dogs survived for over one month.

Of 6 dogs subjected to renal ischemia for 4 hours, 3 lived for over one month and 3 died. The 3 dogs that died survived 4 days, 4 days and 10 days, and the blood urea nitrogens were respectively 157, 182 and 320mg/100 cc at death.

Thus it would appear that renal ischemia for over 3 hours is necessary before the damage to the kidney is sufficient to produce a renal death. [Work done under contract with the Office of Scientific Research and Development.]

A comparative study of androgen and 17-ketosteroid excretion in men. GREGORY PINCUS, ZAREH HADIDIAN AND MARY YEATON (by invitation). Worcester Foundation for Experimental Biology, Shrewsbury, Mass., and the Memorial Foundation for Neuro-Endocrine Research, Worcester, Mass. Simultaneous measurement has been made of the 17-ketosteroid content and androgenic activity of the neutral ketonic fraction of the urines of men of various ages. The androgenic activity, like the 17-ketosteroid titer, varies diurnally, being minimal in urines excreted during sleep and maximal in the morning hours.

Androgenic activity declines with increasing age whereas the 17-ketosteroid output level tends to be maintained at least through the 6th decade in normal healthy men.

The androgenic activity of the non-ketonic neutral fraction of men's urine tends to be in fairly constant ratio to the activity in the neutral ketonic fractions, varying from 3% to 10% of the ketonic androgen.

Similar studies of psychotic men reveal a relatively low androgen output declining notably with age, accompanied by a declining 17-ketosteroid output.

The significance of these findings as indices of adrenal and testis steroid production will be discussed.

The relationship between measures of night vision and dark adaptation. ERNEST A. PRISON

AND A. CHAPANIS (by invitation). *Aero Medical Lab., Air Technical Service Command, Wright Field, Dayton, Ohio*. The necessity for evaluating night vision during the war raised certain fundamental questions regarding the best means of accomplishing such evaluation. The physiology of dark adaptation had been adequately investigated, but little had been done to relate measures of dark adaptation to form perception at illumination levels encountered outdoors at night. Investigations were undertaken to determine the correlation between light perception thresholds and visual performance as measured by perception of forms of different sizes at illumination levels such as occur at night. The light range at which form perception measurements were made varied from 3.6 microlamberts to 0.008 microlamberts. The form size was varied as necessitated by the illumination level and ranged from a standard character (Landolt ring) the maximum diameter of which subtended a visual angle of $\frac{1}{3}$ degree (requiring visual acuity of 20/120) to one subtending a 2° visual angle.

Results on 33 subjects show that there is no correlation between light perception threshold measurements and form perception over the illumination range studied. In correlations of form perception there appears to be a dividing line at an illumination level of approximately 0.5 microlamberts. Correlations above or below this illumination level are very good, but correlations across this level are less good. These data can be explained by the fact that both rods and cones may function above this level, whereas only rods function below this level. This information was used in the design of night vision testers for the Army Air Forces.

Factors determining pH and titratable acid of the urine. R. F. PITTS AND W. D. LOTSPEICH (by invitation). *Dept. Physiology, Cornell Univ. Medical College New York, N. Y.* (Read by title). Urine pH in the dog varies between limits of 4.8 in acidosis and 8.0 in alkalosis. The titratable acid of the urine varies from the equivalent of 6,000 cc of N/10 acid per day in acidosis to negative values in alkalosis. The major factors which determine the pH and titratable acidity of the urine follow: (1) the plasma concentration of bicarbonate, (2) the buffer content of the urine, and (3) the strength of the buffer acid excreted.

Above the threshold for frank excretion (25 to 30 mM BHCO_3/L of plasma) the quantity of BHCO_3 excreted per 100 cc of glomerular filtrate increases in linear proportion to plasma concentration to plasma concentration. The urine becomes increasingly alkaline to a maximum observed pH of 7.96 when the urine contains large quantities of BHCO_3 (up to 200 mM/L). Below the BHCO_3 threshold, essentially all BHCO_3 is reabsorbed and the urine may be as acid as pH 4.8. In the absence

of excretion of fixed buffer acids, however, the titratable acidity of the urine is negligible

In acidosis the rate of excretion of titratable acid varies in proportion to the rate of excretion of buffer, increasing to an observed maximum of 6,000 cc of N/10 acid per day, when as much as 1.4 mols of phosphate are excreted per day. Titratable acid in contrast varies inversely with the strength of the buffer acid excreted. [Aided by a grant from the John and Mary Markle Foundation]

The renal excretion and reabsorption of bicarbonate. R. F. PITTS AND W. D. LOTTSCH (by invitation) *Dept of Physiology, Cornell Univ Medical College New York, N. Y.* The renal excretion and reabsorption of bicarbonate has been studied in 24 experiments on five trained female dogs whose plasma concentrations of bicarbonate were varied from 10 to 70 mM/L. Bicarbonate in plasma and urine was calculated from CO_2 content (Van Slyke method) and pH (condenser type glass electrode) by the Henderson Hasselbalch equation. Glomerular filtration rate was assessed by the creatinine clearance. Plasma bicarbonate was reduced by the oral administration of ammonium chloride for several days prior to the experiment. Plasma bicarbonate was elevated by infusion of sodium bicarbonate solutions.

At plasma bicarbonate concentrations below 20 mM/L essentially all of the bicarbonate filtered through the glomeruli was reabsorbed by the renal tubules (99% plus). At plasma bicarbonate concentrations above 30 mM/L frank excretion of bicarbonate occurred, and the rate of tubular reabsorption of bicarbonate in mM/min was essentially independent of plasma concentration, averaging 2.5 mM/100 cc of glomerular filtrate. [Aided by a grant from the John and Mary Markle Foundation]

Motion picture demonstration of the neurologic and reflex status of the human with completely divided spinal cord. J. LAWRENCE POOL AND E. SCARFF (Introduced by Fred A. Mettler) *Dept of Neurology, College of Physicians & Surgeons, Columbia Univ, N. Y. C.* Moving pictures demonstrate the type and severity of mass involuntary contractions, and tendon and plantar reflexes in patients having proven complete transection of the spinal cord for 6 to 18 months. One patient is shown during a "spinal cord convulsion." Others are shown before and after surgical lysis of the scarred distal stump of the traumatically divided spinal cord, and one case is shown before and after bilateral cordotomy of the dorsal columns at D10 and D12 (for alleviation of severe flexor spasms of the lower extremities). Finally photographs of an operation are presented which demonstrate that mass flexor spasms below the level of the cord transection may be elicited (a) by gentle traction on the scarred adherent tip of the distal stump of the spinal cord, and (b) by electrical stimulation

of the dorsal columns below the level of the transection.

Adverse influence of increased oxygen pressure on malarial parasites in vitro and in vivo. RICHARD J. PORTER (by invitation) AND JOHN W. BEAN. *Depts of Tropical Diseases and Physiology, Univ of Michigan, Ann Arbor, Michigan.* Previous studies (this journal 4 p 6, 1945) showed reduction in viability of *Plasmodium lophurae* in blood equilibrated with oxygen at elevated pressures. The present investigation confirms and extends these observations.

By means of chick inoculation, the viability of parasites in duck or chick bloods exposed to oxygen at various pressures was compared with that in control bloods kept under room conditions. Exposure to oxygen for six hours reduced parasite viability markedly (86 per cent or more below that of controls) at 30 to 60 lb gauge but not appreciably at 15 lb. Exposure for 12 hours gave moderate reduction at 15 lb but no reduction at atmospheric pressure.

Previous *in vivo* studies revealed no detectable effect on the proportion of parasitized erythrocytes in infected chicks given repeated short exposures to oxygen at 50 and 90 lb gauge. Because of the toxicity of these pressures, the present studies have utilized pressures below 15 lb. Six to eleven chicks were treated in each of six experiments. Infected chicks were kept five or six days in oxygen at atmospheric pressure continuously (except one-half hour daily for feeding) or at 300 to 500 mm mercury gauge for about ten hours a day. At the peak of infection, the proportion of parasitized erythrocytes in test birds was 64 to 86 per cent lower than that in controls.

The data indicate that increased oxygen pressure enhances the destruction of *Plasmodium lophurae* in drawn blood and suppresses the parasitemia in infected birds. [Work done in part under contract with the Office of Scientific Research and Development]

The pressure-volume diagram of the thorax and lung. H. RAHN, A. OTIS (by invitation), AND W. O. FENN. *Dept of Physiology, School of Medicine and Dentistry, Univ of Rochester, Rochester, New York.* This diagram relates the maximum voluntary inspiratory or expiratory pulmonary pressure, P , as well as the relaxation pressure of the chest, P_r (as abscissae) to various lung volumes (as ordinates). The difference between P and P_r represents the maximal inspiratory or expiratory muscle forces, P_m , at any specific lung volume. Thus $P_m = P - P_r$. Changes in the level of the tidal and residual air with pressure breathing can be plotted on this diagram as well as changes in the maximum positive and negative pressures that can be voluntarily exerted at altitude.

The relaxation pressure is the resultant of two

major components which oppose each other at most lung volumes, the positive lung elasticity, P_l , and the negative "chest" elasticity (including the diaphragm etc.), P_c . Thus $P_r = P_l + P_c$. P_r can be altered by posture. From P_r and the simultaneous change in peripheral venous pressure between two different lung volumes the change in P_l can be computed.

The elastic work of breathing at ambient pressure can be determined from the slope of the relaxation pressure curve (70 cc/cm H_2O). If the tidal volume, T , is expressed in cm^3 the work (gm cm) is equal to $T^2/140$. A formula to include the viscous work has been derived. The work so calculated at different rates of breathing parallels the total energy expenditure as determined by Liljestrand (1918). The efficiency of the work of breathing is about 5 per cent. [Work done under contract with the Office of Scientific Research and Development.]

Clinical gonadotropic therapy complicated by antihormone formation. A. E. RAKOFF (by invitation) and J. H. LEATHEM, *Jefferson Medical College and Hospital and Rutgers Univ.* The formation of antihormones against equine gonadotropin in the human is known and the availability of other gonadotropins for clinical use warrants similar tests. In this investigation a combination of sheep anterior pituitary extract and chorionic gonadotropin (Synapoidin) was studied in 25 patients. This hormone was administered in the treatment of sterility, amenorrhea or functional bleeding. In general, the gonadotropins were injected in 1 cc (15 rat synergy units) amounts 3 times weekly for the first 2 weeks of each cycle. The presence of antihormones against synapoidin was estimated by the ability of the patient's serum to inhibit, in rats, the ovarian stimulating action of a uniform dose of hormone. Normal serum does not have an inhibitory action. Furthermore, the sera from 22 patients treated for 2 to 5 months failed to reveal the presence of antihormones. In 3 cases, however, which were treated for functional bleeding for more than 6 months the presence of antihormones could be correlated with the clinical response, that is, the failure of the patient to continue to respond to therapy coincided with the time at which antihormones were detectable.

The effect of calcium pantothenate on survival in adrenalectomized rats. ELAINE P. RALLI, *Dept. of Medicine, New York Univ. College of Medicine.* At 30 days of age black rats were placed on diets deficient in the filtrate factors of vitamin B. After 30 days on the diet they were adrenalectomized and were then treated as follows: Group 1, 105 rats were continued on the deficient diet; Group 2, 119 rats received the deficient diet but were injected daily with either (a) adrenal cortical extract or (b) desoxy corticosterone acetate; Group 3, 78 rats received the diet supplemented with calcium pantothenate. All 3 groups received a 1% solution of NaCl ad lib.

Groups 4, 5, 6, 86 rats, were treated in a similar manner as to diet and hormone therapy but were given no NaCl solution after adrenalectomy. Survival for the groups was: Group 1, 119 days \pm 5.4; Group 2a, 16 days \pm 7.2; Group 2b, 16 days \pm 6.8; Group 3 receiving calcium pantothenate survived much longer, 85% survived 50 days, 57% survived 100 days, 41% survived 150 days, 28% survived 200 days and 12% survived 250 days. The survival in the groups receiving no salt was: Group 4, 6 days \pm 2.5; group 5, 11 days \pm 5; group 6 (calcium pantothenate) 5.6 days \pm 0.3. Besides autopsies the completeness of adrenalectomy was tested in group 3 by depriving 17 rats of NaCl after varying periods on the diet. These all lost weight and died. In conjunction with NaCl, calcium pantothenate is essential for survival in adrenalectomized rats. Hormone therapy does not result in prolonged survival if either substance is lacking in the diet.

Determination of the circulating cell volume by a partial washout method. ANTONIO RAMIREZ and DINA B. RAPPAPORT (introduced by Hampden Lawson), *Dept. of Physiology, Univ. of Louisville School of Medicine, Louisville.* Blood was drawn from splenectomized barbitarized dogs by free arterial bleeding in unit volumes of 10 cc/kg, and immediately replaced with an equal volume of either saline or gelatin solution. This procedure was repeated at intervals of 3 minutes until death occurred, or until 6 to 12 replacements had been made. The volume of cells obtained in each bleeding was determined by centrifugalization. The volumes were found to decline exponentially, death usually occurring when the hematocrit in drawn blood had fallen to some value in the neighborhood of 5%. Plasma volume was determined as the dilution volume of the dye T-1824 at the beginning of each experiment. Except for the preliminary studies, the washout was usually terminated before death, to permit redetermination of plasma volume. Total circulating blood volume was assumed to have remained constant through the washout when the plasma volume at the end exceeded the initial plasma volume by an amount equal to the volume of cells drawn. In such experiments the total cell volume was calculated as the sum of an infinite declining geometrical series, using the conventional formulas. Where evidence was obtained for a change in the total circulating blood volume, it was necessary to make a small correction in the slope of the series. The volume of cells determined in this way was from 70 to 95% of the volume estimated at the beginning of the washout from the plasma volume and the hematocrit in drawn blood.

Some local processes concerned in the genesis of traumatic shock. ROBERT W. RAMSEY,¹ TERPINE

¹ Present address—Department of Physiology and Pharmacology, Medical College of Virginia, Richmond.

ADLER (by invitation) *Dept of Physiology, School of Medicine and Dentistry, Univ of Rochester, Rochester, New York* A muscle or muscle group of one hind limb of a rat was crushed with forceps under anesthesia. Twenty-four hours later, five to nine muscle groups from both the experimental and the control hind limb were dissected and separately weighed and their per cent dry weight determined. These figures can be used to calculate the ratio of the excess water moved into a muscle on the experimental side as compared to its corresponding muscle on the control side.

With the above and other data it was established that a crushed muscle swells and then liberates an exudate, the composition of which is similar to a dilute plasma solution containing some hemoglobin. This exudate by differential pressure spreads up and down the fascial plane associated with the traumatized muscle. In so doing it causes marked secondary swelling or wetting of uninjured muscle, skin, and connective tissue, which is in functional relationship with this fascial plane. Any tissue which is not in the same fascial plane is quite unaffected.

If an artificial exudate (dilute, plasma) in quantity and protein content equal to that exuded by a crushed muscle is injected into the corresponding fascial plane of a normal animal, the same order, magnitude, and time of appearance of wetting of the various muscle groups develops, that would have developed if the appropriate muscle had been traumatized.

It is concluded that no toxic factor in the ordinary sense of the word, is involved in the initial (24 hours) swelling of a traumatized limb [*Work done under contract, sponsored by CMR, between O S R D and the Univ of Rochester*].

Enumeration of functional sweat glands in the human WALTER C RANDALL *St Paul Univ School of Medicine* A simplified starch-iodine test has been devised which permits precise enumeration of active sweat glands as well as demarkation of sweating and non-sweating areas. The method eliminates the necessity of starch powders and requires no apparatus except iodine and white paper containing minute amounts of starch. A dilute solution of iodine (3%) is painted over the test area and allowed to dry. A blank piece of paper is then pressed lightly over the area for 20 to 30 seconds. It is desirable to use a paper with smooth, hard finish to prevent diffusion of the record. With the paper in place, water secreted from the sweat pore places the iodine and starch (in the paper) in solution thereby producing a definite blue-black spot on the paper. Records thus produced are clear and sharp and well adapted to studies of general patterns of sweat gland

activity over the body surface, the number of glands participating under varying physiological conditions, and the character of sweat responses following denervation or pathology.

Using this technique a comparison of the number of glands involved in sweating under different sudorific stimulation was made. From theoretical considerations cholinergic drugs might be expected to produce maximal stimulation of the sweat glands. Experimentally, relatively extreme thermal stimulation provided by hot tub bath was required to activate as many glands on the forearm as was obtained by acetyl-beta-methylcholine.

The metabolism of the kidney in experimental renal hypertension SIGMUND B RASKA (introduced by Charles O Warren) *Dept of Pharmacology, Cornell Univ Medical College, New York, N Y* A direct relationship appears to exist between the oxidative power of the kidney and the formation of hypotensive substances. This relationship is indicated by 1) the increased concentration and increased activity of various respiratory enzymes in the remaining kidney of unilaterally nephrectomized dogs compared to the activity of the same respiratory enzyme systems of the excised kidney of the same animal or of normal kidneys of normal dogs. There is a similar increase in the activity of oxidative enzymes in the uninjured kidney of dogs in which the function of one kidney has been modified by silk perinephritis or partial constriction of its renal artery. In the latter there is a decreased activity of the oxidative biocatalysts (Raska, S B, J Exp Med, 1945, 82: 227). 2) Extracts prepared from the remaining kidney of dogs or rabbits one week to three months after unilateral nephrectomy were more effective in lowering the blood pressure of hypertensive rabbits and rats when given parenterally than extracts prepared by the same method from the excised kidney of the same animal or from normal kidneys of normal dogs or rabbits. Similar results were obtained with extracts of the uninjured kidney of dogs when the function of the opposite kidney was altered by wrapping in silk or partial constriction of its renal artery.

It was found that the increase in hypotensive activity of these extracts was largely due to an increase of a dialyzable blood pressure lowering fraction. Hypotensive substances of renal origin are probably the products of oxidative processes. They are formed in increased amounts in the compensating kidney.

A method for determining reduction time of cutaneous blood, and its significance in relation to certain physiological changes. LOUISE H RAY (by invitation), GEORGE B RAY (deceased) AND J RAYMOND JOHNSON *Dept of Physiology, Long Island College of Medicine, Brooklyn, N Y* A simple method has been developed for measure-

ment of the time required for a standard change in the spectrum of superficial blood after sudden occlusion of the circulation. This time is called the reduction time. The apparatus is compact and the procedure technically easy. Observations may be made in the field, at the bedside, or under a variety of other conditions.

Reduction time is not a simple value, but a function of several variables. Alveolar oxygen tension, systolic and diastolic blood pressures, basal metabolic rate and activity of the autonomic nervous system all affect reduction time.

Changes in reduction time also occur with stress. Thus, such a mild form of bodily strain as breath-holding causes, in the normal subject, a marked decrease in reduction time. This change after breath-holding has been found to be a sensitive index of the condition of a subject.

A series of test-retest experiments was performed on forty-one medical students under controlled conditions. The correlation coefficient between the results of the first and second tests was 0.81. [Work done under contract with the Office of Scientific Research and Development.]

In vitro examination of synovial dynamics with a needle electrode. C. I. REED AND NORMAN R. JOSEPH (by invitation). *Dept. of Physiology, Univ. of Illinois, Chicago Colleges*. By means of needle reference electrodes, previously described (Joseph and Homburger, *Fed. Proc.* 4: 38, 1945), it has been possible to measure pH simultaneously in the femoral vein and in the synovial cavities of both knees of anesthetized dogs. Experimental procedures included injection of substances into the blood stream, tetanization of the femoral nerve, passive motion, massage, injection of substances into the synovial cavity. The pH changes were used merely as an indicator of the responses of the synovial tissues to physiological influences.

X-ray diffraction studies on bones. C. I. REED AND B. P. REED (by invitation). *Dept. of Physiology, Univ. of Illinois, Chicago Colleges*. (Read by title.) In a previous report on x-ray diffraction studies on bones of rachitic rats, it was concluded that vitamin D alone, when added to the rachitogenic diet, could correct the disturbance of the crystal pattern of the apatite in the bones. Since the diet used was deficient in other respects, the experiment was repeated with completely synthetic diets. The results confirm the earlier conclusion that vitamin D alone can correct for a variety of dietary deficiencies which are capable of disorienting crystal structure in bone.

Evidence that the major portion of the gastric potential originates between the submucosa and mucosa. WARREN S. REHM. *Dept. of Physiology, Univ. of Louisville School of Medicine, Louisville, Ky.* In dogs anesthetized with amytal, non-polarizable electrodes were placed opposite each

other on the serosal and mucosal surfaces of the stomach. In previous studies (Am. J. Physiol., 140: 720, 1944) it was found that ethyl alcohol or ether when applied to the mucosa resulted in a marked decrease in the potential difference across the stomach. In the present studies it was found that there was no change in the potential difference when these same agents were applied to the serosal surface. These findings indicate that the potential probably originates somewhere in the mucosa. Further evidence on this point was obtained by placing an electrode in the submucosa. An incision was made through the outer muscular layers and a glass capillary containing Ringer's solution was inserted into the submucosa for several centimeters parallel to the surface of the stomach. The capillary was connected to a non-polarizable electrode and mucosal electrodes were placed on the stomach opposite the opening of the capillary. The potential difference between the submucosal and the mucosal electrodes was found to be essentially the same as that between the serosal and mucosal electrodes. The potential difference between the submucosal and serosal electrodes was only a few millivolts. The effect of histamine and thiocyanate on the potential differences between the three electrodes was studied. It was found that changes in the potential difference between the submucosal and mucosal electrodes closely paralleled those between the serosal and mucosal electrodes.

Calculation of the arterial uptake and stroke volume from the pressure pulse contour. JOHN W. REMINGTON AND W. F. HAMILTON. *Dept. of Physiology, Univ. of Georgia School of Medicine, Augusta, Georgia*. The main arterial branches of five dogs were clamped, and pressure pulses recorded after intra-aortic injections of known volumes of saline. The ascending branches were opened and the experiment repeated. The uptake and drainage of the two systems were calculated from injected volumes and pressure pulses. Similar data were obtained for arteries supplying the viscera, and the hind legs. The systolic uptake of the dog aorta is only 45% of that of the whole arterial tree. The arteries arising from the arch take up 33%, visceral arteries 9%, and those to the hind legs the remainder. From volume-pressure curves for peripheral arteries, the uptake of the three peripheral beds was estimated at different diastolic and pulse pressures. Pressures obtaining in each bed at the end of systole were determined by measuring back on the aortic root pressure pulse contour from the incisura, employing pulse wave transmission times. Using the pressure rise from diastolic to that obtained at the end of systole, the total arterial uptake was measured as the sum of the uptakes of the separate beds. Drainage was estimated and partitioned between systole and diastole on the basis of pressure-time areas. Systolic

uptake plus drainage should equal the stroke volume. Stroke volumes derived from pulse contours are being compared with those found by the injection method. The agreement, at present, is encouraging.

Influence of the vascular bed on the pattern of oxygen tension in the cerebral cortex. ANTOINE RÉMOND (by invitation), P. W. DAVIES (by invitation) AND D. W. BRINK. *Johnson Foundation, Univ of Pennsylvania, Philadelphia*. When one traverses the cat cortex with the oxygen electrode described by Davies and Brink, one encounters gradients of oxygen concentration corresponding to the pattern of the vascular bed. The tension varies between 100 mm Hg (arterial blood) and a value near zero. The high value of cortical metabolism is evidenced by the fact that the oxygen tension generally falls to half this value at from 15 to 30 microns from an arteriole. One cannot speak of an "oxygen tension of the cortex", for each region has its special value.

The value of the tension of arterial blood rises from 100 to 700 mm when oxygen is breathed instead of air (600% increase). In veins it rises from 40 to 50 mm (20% increase). Systematic measurement of this increase in the cerebral vessels shows that those venules coming from deeper layers, which have a gain of 20 to 30%, contain blood which has been fully unloaded. The superficial venules on the other hand behave as if they contain as much as 70% arterial blood.

This can be explained 1) by the marked dilatation of the superficial vessels which appears after resection of the dura. The blood passing more rapidly through these vessels loses less oxygen, 2) by the possible differences in the metabolism of the regions traversed.

These facts permit one to make a functional classification of the vessels based on their oxygen content, contrasting with the usual anatomical classification.

Interaction of nerve impulses in the gray matter as a mechanism in central inhibition. BIRDSEY RENSHAW. *Laby of The Rockefeller Inst for Medical Research, New York City, and Oberlin College, Oberlin, Ohio*. Motoneurons supplying the quadriceps muscle in anesthetized cats discharge 1.0–1.1 msec after a sixth lumbar dorsal root (L_6 DR) volley arrives at the spinal cord. Detectable inhibition of the discharge is apparent if an L_7 DR volley arrives at the cord 1.0–1.1 msec before the motoneurons discharge. Both intervals are briefer by ca. 0.3 msec if estimated from the time of arrival of the dorsal root impulses in the vicinity of the quadriceps motor nucleus. The inhibition rapidly increases to become complete as the interval at which the L_7 DR volley precedes the L_6 DR volley increases.

The potential changes recorded in the motor

nucleus during the synaptic delay associated with the excitation of the motoneurons by an L_6 DR volley are modified by a simultaneously arriving or slightly antecedent L_7 DR volley. This finding suggests the interpretation that during the synaptic delay interaction occurs between impulses in the terminal branches of the two groups of dorsal root fibers.

A strong presumption that at least part of the interaction is in fact between the two groups of premotor fibers, and that this interaction underlies the "direct" inhibition of the quadriceps motoneurons by an L_7 DR volley, is created by the finding that the responsiveness of the motoneurons as tested by the size of their antidromically evoked somatic action potential is not altered at intervals following an L_7 DR volley at which the reflex motor discharge evoked by an L_6 DR volley is virtually abolished.

The bulbar inhibitory mechanism in concussion. R. RHINES (by invitation), H. W. MAGOUN AND W. F. WINDLE. *Dept of Anatomy and Inst of Neurology, Northwestern Univ Medical School, Chicago*. (Read by title.) The widespread involvement of reflexes in experimental cerebral concussion can be attributed to alterations in individual reflex arcs or to alteration of a common brain mechanism influencing reflex activity (Denny-Brown and Russell, 1941). The recent demonstration of a bulbar inhibitory mechanism with such potentialities (Magoun and Rhines, 1945), led to its examination in concussion.

In an examination of the patellar reflex in concussion in the anesthetized cat, some motor discharge occurred at the blow and a brief impairment of the reflex was followed by a pronounced and longer lasting hyperreflexia before return to normal. A reversible depression of the excitability of the bulbar inhibitory mechanism in general paralleled this reflex augmentation, suggesting that release from bulbar inhibition may have been a factor in its production. [Work done under contract, sponsored by CMR, between OSRD and Northwestern Univ.]

Inhibition of procaine induced convulsions by its split products. R. K. RICHARDS, M.D., *Dept of Pharmacology Abbott Labs, N. Chicago, Ill*. The bacteriostatic action of sulfonamides is inhibited by the presence of paraminobenzoic acid (PABA). While the exact mechanism of this effect is still disputed, there is evidence for the competitive nature of this antagonism. It also has been established that compounds, particularly local anesthetics, which are derived from PABA, have a similar inhibiting effect upon sulfonamides. The purpose of our investigation was to establish whether the convulsive action of procaine, being a PABA derivative, can be inhibited by PABA itself.

100 mg /kg of procaine HCl given i m to guinea pigs produced nonfatal convulsions in approximately 85%. If this injection was preceded by IP administration of 400 to 600 mg /kg P A B A as sodium salt, convulsions were reduced to 56% and 13% respectively. Use of other P A B A derivatives showed specific relations between their structure and the degree of protective action exerted. It was also found that the other part of the procaine molecule, diethylaminoethanol (D E A E) in a dose of 400 mg /kg (as the hydrochloride) reduced procaine convulsions to approximately 8%. Certain other amino alcohols having a structure similar to D E A E show some protective action. It could be demonstrated that neither P A B A nor D E A E exerted a general anticonvulsant action against other convulsive drugs.

The protective action exerted by both compounds can be best explained on the basis of competitive inhibition of the two procaine split products with procaine itself on certain receptors in the metabolism of the C N S.

The indirect determination of partial pressures in alveolar air. R. L. RILEY (by invitation) AND J. L. LILIENTHAL, JR. *School of Aviation Medicine, U S Naval Air Station, Pensacola, Fla* (Read by title). The errors inherent in direct sampling of alveolar air make the standard methods unreliable for studies during exercise. An indirect method has been developed for calculating the alveolar gas pressures and is based on two assumptions for which corroborative evidence exists: 1) the arterial $p\text{CO}_2$ equals the integrated mean of the entire range of $p\text{CO}_2$ existing throughout all perfused alveoli during a series of respiratory cycles (i.e., alveolar $p\text{CO}_2$ equals arterial $p\text{CO}_2$), and 2) the alveolar respiratory quotient equals the expired air respiratory quotient. These assumptions permit the use of the familiar alveolar air equation to calculate the alveolar $p\text{O}_2$:

$$\text{alveolar } R Q = \frac{\text{alveolar } p\text{CO}_2}{\text{tracheal } p\text{O}_2 - \text{alveolar } p\text{O}_2}$$

Introducing the assumptions above

$$\text{expired air } R Q = \frac{\text{arterial } p\text{CO}_2}{\text{tracheal } p\text{O}_2 - \text{alveolar } p\text{O}_2},$$

and re arranging

$$\text{alveolar } p\text{O}_2 = \text{tracheal } p\text{O}_2 - \frac{\text{arterial } p\text{CO}_2}{\text{expired air } R Q}$$

Thus the effective alveolar pressures are calculated readily by determining a) arterial $p\text{CO}_2$, b) concurrent expired air $R Q$, and c) inspired $p\text{O}_2$.

Thirty-one such determinations have been made at sea level and during anoxia and compared with Haldane Priestley alveolar samples on five trained subjects. The H-P alveolar $p\text{CO}_2$ averaged 4.4 mm Hg higher at rest and 12.4 mm higher during

exercise than those calculated by the indirect method. The H-P alveolar $p\text{O}_2$ averaged 7.7 mm (rest) and 18.4 mm (exercise) lower than the direct determinations. [The opinions or assertions contained herein are the private ones of the writers and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.]

A study of Q-T interval in various species. JANE SANDS ROBB *Dept of Pharmacology, Syracuse Univ, Syracuse, N Y*. For eleven species Q-T duration has been measured. Q-T-cycle relationship plotted on ordinary graph paper produces a hyperbolic curve. When plotted on double logarithmic paper presents a straight line. Reconstructing serial sections of guinea pig hearts, Kaylor and Robb find that limited areas of cardiac muscle are supplied from one strand of conducting tissue. The theory that numerous limited areas are depolarized and repolarized simultaneously is supported by generally accepted readings of "initial negativity." It is suggested that the size of the area supplied by individual conduction system branches and not the total mass of the heart is a determinant of Q-T duration. This interval not only varies according to metabolic rate within one species, but also with metabolic rate from one species to another. Cellular metabolism (altered by various physiological and/or pathological conditions) may govern the rate of depolarization and repolarization. Only certain heart rates are "normal" for a species or for an individual within a species. Rates outside this "normal" range (say 70-90 per minute for an adult man) are sometimes caused by conditions which themselves alter Q-T duration. Thus rates of less than 60 may be caused by vagal stimulation which itself makes Q-T shorter than would be expected for the coincident lengthening of cycle. Similar mechanisms may skew the data for any species. Once the Q-T parameter has been established, any deviation from it will require explanation.

The cardiac component of the orienting reflex. JANICE ROBINSON (by invitation) AND W. HORSLEY GANTT *Parlovian Laby, Phipps Clinic, Johns Hopkins Univ*. The effect of the stimulus itself before it is made a signal for an unconditional reflex is known as the orienting reflex (OR). Motor responses, salivation and changes in heart rate were taken as measures of the OR to neutral auditory and visual stimuli. As the neutral stimulus is repeated the initial changes in heart rate progressively decrease, in contrast, when the neutral stimulus becomes conditioned by reinforcement (with food or shock) the change in heart rate becomes greater and constant. The motor components of the OR (vocalization, movement of ears, turning toward stimulus, etc.) the less accurate indices than the cardiac changes, show

a parallel pattern of extinction with repetition of the stimulus. The heart rate is the most significant index of OR, showing a high correlation between animals, for different stimuli and with the motor components. Furthermore it can be measured precisely. The cardiac reflexes (orienting and conditional) vary with each dog, some showing acceleration, others deceleration, tho the pattern is similar for OR and cr. The OR is subject to conditional inhibition by repetition, its reappearance later, after conditioning, is a symptom of nervous strain, probably a result of disinhibition from agitation. The sensitivity of the cardiac reflexes is shown by their correlation with the OR as well as by their almost immediate transformation into crs when the signal is reinforced.

Thermal balance of men working in severe heat *SID ROBINSON AND S. D. GIERING* (by invitation) *Dept of Physiology, Indiana Univ., Bloomington, Indiana*. In a series of 6 hour experiments men who were acclimatized to work in the heat walked on a treadmill at a metabolic rate of 190 Cal /m²/hr maintaining water balance by drinking 0.1% salt solution. In an air temperature of 50° C with a wet bulb temperature of 28° C the men, clad only in shorts, shoes and socks, maintained thermal equilibrium with rectal temperatures of about 38°C from the 2nd through the 6th hours. Wearing Army tropical uniforms in the same work and environment they attained thermal equilibrium from the 2nd through the 4th hours and then experienced a secondary rise in rectal temperature to above 39°C by the end of the 6th hour. Reducing the work so that the metabolic rate was 125 Cal /m²/hr made it possible for the clothed men to continue in equilibrium through the 6th hour. At the higher rate of work the men in shorts had the characteristic secondary rise in body temperature when the wet bulb temperature was raised to 30°C. The rise in body temperature occurring in the last two hours was always associated with decreased evaporation because of a decline in sweating.

When the clothed men worked at a metabolic rate of 190 Cal /m²/hr with the dry bulb temperature 50°C, raising the wet bulb temperature to 31°C brought them to exhaustion with rectal temperatures of 40°C within two hours, a rise in wet bulb temperature to 32.6°C brought the men in shorts to exhaustion with rectal temperatures of 40°C within 90 minutes. [*This work was done under a contract, with the Office of Scientific Research and Development*]

The effect of oxygen, altitude, and exertion on breath-holding time *S. RODBARD*¹ A total of 1581 determinations of voluntary breath-

holding times was made under various conditions of reduced barometric pressure, of oxygen tension and after exertion on 81 volunteers. The hold was determined from the time of a single deep inspiration until the following exhalation. Subjects were instructed to hold the breath until a moderate degree of discomfort was experienced.

The average hold at rest at ground level while breathing air was 70 seconds. Hyperventilation of air at ground level for 30 seconds increased the hold to 100 seconds, hyperventilation of pure oxygen for 30 seconds doubled the hold.

The hold was reduced progressively with "altitude" in the decompression chamber while breathing ambient air, falling to 40 seconds at 18,000 feet. On breathing pure oxygen at ground level, the hold was increased to 95 seconds, with increasing altitudes this enhancing effect of oxygen was progressively diminished so that at 23,000 feet the hold averaged 70 seconds, and at 38,000 feet the hold was 45 seconds.

A preliminary burst of exercise for 15 seconds caused a reduction of the hold which was proportional to the effort, regardless of the per cent oxygen inspired, or of altitude up to 38,000 feet. Exertion equivalent to 1500 foot pounds reduced the hold from an average of 70 to 40 seconds, 3000 foot pounds reduced it to 26 seconds. Even very mild activity such as rising or standing caused a transient reduction in the hold.

It is apparent that the hold depends in large part on the alveolar oxygen and carbon dioxide tensions.

Factors affecting bubble volume in the tissues at various altitudes. *S. RODBARD*¹ (Read by title) Previous studies on decompression sickness suggested that symptoms could be explained most satisfactorily by Bert's thesis that bends result from the presence of bubbles in sensitive tissues. Relative bubble volume has been estimated by the relationship

$$\frac{\text{Volume}_{\text{altitude}}}{\text{Volume}_{\text{sea level}}} = \frac{\text{Bar Pr}_{\text{sea level}} - 47}{\text{Bar Pr}_{\text{altitude}} - 47} \quad (1)$$

where Bar Pr represents barometric pressure in mm Hg and 47 represents body water vapor tension. However, bubbles in the tissues would equilibrate rapidly not only with water vapor, but also with tissue CO₂ and O₂. A more likely formulation of relative bubble size would therefore be

$$\frac{\text{Volume}_{\text{altitude}}}{\text{Volume}_{\text{sea level}}} = \frac{\text{Bar Pr}_{\text{sea level}} - (47 + 40 + 40)}{\text{Bar Pr}_{\text{altitude}} - (47 + 40 + 40)} \quad (2)$$

where 47, 40, and 40 represent tissue tensions of water vapor, CO₂ and O₂, respectively. The dif-

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ference, Bar Pr - (47 + 40 + 40) represents bubble N_2 tension, except at extreme altitudes where tissue and surface tension factors become significant

Equation (1) indicates that a bubble in the tissues at ground level would expand to 7 volumes at 38,000 feet, while equation (2) shows that it would expand to 25 volumes. The latter equation shows a marked increase in volume around 30,000 feet, at which the incidence of bends markedly increases. It also coincides with the rate of relief from bends pain during descent from 38,000 feet

Changes of nerve properties near a killed region. A ROSENBLUETH and J GARCIA RAMOS (by invitation) *Section of Physiology, Instituto Nacional de Cardiologia de México*. In cat peroneal nerves the changes of properties near an injury (crushing or clean section) are as follows: excitability subnormal, refractoriness (absolute and relative) prolonged, conduction velocity slow, spike potential amplitude small, duration unchanged. With adequate electrode arrangement, anodal polarization results in a decrease, cathodal in an increase of the spike amplitude. These changes appear immediately upon injuring the nerve. They are due to the nearness of the injury and are not caused by the demarcation potential or by flow of ions. They are first stable. Later occurs a progressive further impairment due to the progressive death of the fibers from the injury toward the normal regions.

There is no "healing." The increasing diphasicity of "monophasic" responses and the decreasing demarcation potential are artifacts due to the prolongation of the electrode on injured tissue by the dead fibers into the nerve trunk and to the consequent effective contact with the external surface of intact elements.

The effect of histamine, administered intravenously in increasing concentration, on the pain threshold of normal subjects. GRACE M ROTH, *Section on Clinical Physiology, Mayo Clinic, Rochester, Minnesota*, DAN Y BURRILL (by invitation), *Northwestern Univ Dental School* and A C IYR, *Dept of Physiology, Northwestern Univ Medical School, Chicago, Illinois*. The method of Goetzl, Burrill and Ivy was used to determine the pain threshold of ten normal subjects. A slow infusion of histamine di phosphate, containing 1 mg of histamine base in 250 cc of physiologic saline solution (1:400,000 dilution), was administered subsequent to a control infusion of physiologic saline solution. Blood pressure, pulse rate and pain threshold were determined simultaneously at five minute intervals as the quantity of histamine base injected was increased from 0.004 mg per cubic centimeters to 0.02 mg per cubic centimeters per minute.

The complete series of observations was made

twice on each of nine subjects and three times on the tenth subject. There was a lowering of the pain threshold of four subjects, no significant change in three subjects and an elevation in the other three subjects.

Inhibition of the emetic effect of intravenous glutamic acid in dogs. L W ROTH (by invitation), R K RICHARDS and F R STEGGERDA *Dept of Pharmacology, Abbott Lab., North Chicago, Ill*. (Read by title). When 1+ glutamic acid, as a 5% solution with a pH of 1.1, was infused into 20 dogs at a rate of 10 mg/kg/min, vomiting occurred at an average dose of 136 mg/kg. There were no signs attributable to acidity effects. Various agents were tried in an attempt to delay or prevent the vomiting reaction. Atropine, d-desoxyephedrine, or pyridoxine with thiamine were found to have no significant effect. In 10 dogs injected i.v. with 2 mg/kg of Nembutal, 10 minutes before the glutamic acid infusion, the average amount of glutamic acid necessary to produce vomiting was raised to 219 mg/kg, which is a statistically significant difference. This amount of Nembutal has no detectable sedative action upon the dogs. It was found that dogs will develop a tolerance to the emetic effect of glutamic acid, if the administration is repeated within a few days. This was taken into account in the above experiments by comparing only "first run" experimental results of the different series.

The relation of the deep opercular cortex to taste. THEODORE C RUCH and HARRY D PATTON (by invitation) *Lab of Physiology, Yale Univ School of Medicine, New Haven*. In an initial series of experiments taste deficits as demonstrated by threshold curves for bitter obtained by the preference method failed to occur after bilateral ablation of the free surface of the inferior central region. Definite but transitory disturbances seemed correlated with the degree of destruction of the buried opercular cortex. Gerhardt (*Jour f Psych u Neurol*, 1938, 48: 328) describes in a chimpanzee brain a previously unknown area of granular cortex of the sensory type (Area 6S II gr) in the precentral operculum bordering on the circular gyrus. Analysis of the initial series of lesions by serial sections indicates that this region was in no case bilaterally destroyed. In three experiments destruction of this region was attempted. In Exp 1, it was approached by ablating the motor face area and a severe taste disturbance was manifested but testing was inconclusive due to interference with swallowing. In Exp 2, the horizontal superior border of the lesion passed just below the inferior end of the central fissure. A moderate taste deficit was demonstrable 41-93 days after operation. In Exp 3, Gerhardt's granular cortex was approached by opening the Sylvian fissure, and a strip of operculum bordering on the insula was destroyed by suction. In a determination of the preference

threshold (32-56th postoperative days) bitter solutions, which had been totally rejected before operation, were drunk equally with water. Significant quantities of solutions were accepted which were 16 times as strong as those completely rejected before operation. The degree of permanence of this deficit is under investigation. The maximal taste deficits have occurred when Gerhardt's granular area was ablated and damage to the free opercular surface was minimal. The available evidence suggests that taste is localized neither in the traditional hippocampal area nor in the free cortex of the operculum but in the parainsular area of the operculum. [Aided by a grant from the Fluid Research Funds, Yale Univ. School of Medicine.]

Crash injuries in experimental animals (motion picture) ROBERT F. RUSHMAN (introduced by Herman S. Wigodsky) *AAF School of Aviation Medicine, Randolph Field, Texas*. This motion picture was designed to illustrate the effects of abrupt deceleration on experimental animals. Anesthetized cats were restrained in various ways in carts constructed so that obstructions could be installed which were similar to those found in aircraft cockpits. High speed motion pictures (3600 frames per second) were taken to observe the points of contact and distortion of animals at impact. The pathological lesions produced by the action of decelerative forces are shown in color.

Injuries of the lungs, liver, spleen, mesentery, spine and renal vessels were found which were similar to those encountered at post-mortem on humans following aircraft accidents. Injuries sustained by the lungs were characterized by diffuse hemorrhages into the parenchyma which were most commonly found in the middle and lower lobes. The location of these hemorrhages did not appear to be related to the direction of action of the decelerative force. Areas of emphysema along the lung margins were encountered in a few cases. The lesions found in the liver and spleen usually consisted of linear lacerations of the capsule on the diaphragmatic aspect, extending into the parenchyma and often associated with profuse hemorrhage.

Pressure waves could be seen traversing the anterior abdominal walls of animals in the supine position. There was a great deal of variability in the severity of the injuries sustained by animals exposed to decelerative force under apparently similar conditions.

Physiological reactions of men working in the cold in relation to the amount of clothing worn H. D. RUSSELL (by invitation), H. S. BELDING, and R. C. DARLING *Fatigue Lab., Harvard Univ., Boston, Mass.* Four clothing outfits varying five-fold in insulation value have been worn by men while performing the same uphill walks at 0°F, each exposure lasted two hours.

The men were most comfortable while wearing

one of the two outfits of intermediate weight (11 or 17 pounds). In the assembly of preference average data were: skin temperature, 81°F, rectal temperature, 100.9°F, energy production 7.2 Cals/kg/hr, pulse rate, 133/minute, sweat, 235 grams/hr, and calculated efficiency of sweat for body cooling, 61 per cent.

In the lightest clothing (underwear, socks, and shoes) the men felt cold, but the most striking effect was a suppression of sweating to less than 50 grams/hour, at the same time mean skin temperature fell as low as 64°F, and there was incipient or actual local frostbite, rectal temperature dropped to 98.1°F, and energy production was 8.6 Cal/kg/hr elevated as a result of increased muscle tone and shivering.

In the heaviest clothing (22 pounds) the men felt very hot and the subjects verged on heat exhaustion, mean skin temperature rose to 95°F, rectal temperature to 102.8°F, pulse rate to 180/minute, heat production to 7.9 Cals/kg/hr because of the extra work and "hobbling effect" of carrying the heavy clothing, and sweat to 900 grams/hour, efficiency of the sweat for body cooling was 37 per cent.

Energy loss in the four outfits has been partitioned to determine the relative importance of the various avenues of heat loss.

The lymphatic conveyance of thyroid hormone WILLIAM T. SALTER and WALLACE F. WHITE (by invitation) and E. A. MCKAY (by invitation) *Dept. of Pharmacology, Yale Univ. School of Medicine*. Protein-bound iodine in serum is used routinely to measure net thyroid function. This "hormonal" iodine is incorporated chiefly in the albumin fraction VI of E. J. Cohn's Tiselius tested human plasma preparations. Of a total 52 micrograms of protein-bound iodine per liter of plasma, the two albumin moieties (V and VI) contribute 38. A second peak in the alpha-beta globulin range of this plasma iodine "concentration-spectrum" makes a relatively unimportant contribution to the whole.

How does this protein-bound hormone reach the cells? With the aid of C. K. Drinker protein-bound iodine in dog lymph has been measured. In general, protein-bound iodine in cervical and hmb lymph and in pericardial fluid can be predicted from the presumed albumin content. The inorganic iodine is usually negligible (under 1 µg %) in both serum and lymph. These minute concentrations of iodine can be measured readily in 1-ml samples by the rate of catalytic reduction of ceric ions with arsenious acid. In one dog the protein (in grams-per cent) was 8.3 for serum, 1.6 for pericardial fluid, 2.6 for right cervical lymph, 2.6 for left cervical lymph. Corresponding values for protein-bound iodine in micrograms-per cent were, respectively, 4.6, 1.3, 2.6, 2.8.

The findings emphasize the importance of capillary leakage of albumin in establishing a labile fluid medium by which the tissue cells are bathed with a steady concentration of thyroid hormone

The causation of the latency relaxation ALEXANDER SANDOW *Washington Square College of Arts and Science* The latency relaxation (LR) has been recorded by the piezoelectric, cathode-ray oscillographic method in techniques such that the participation of a mechanical compression wave in the sense of Schoepfle and Gilson (*J Cell Comp Physiol* 26 119, 1945) is excluded In the transverse technique, the LR is obtained by having the pickup stylus press down across a *Rana pipiens* sartorius slung horizontally in air on a special muscle holder The stylus acts as cathode The depth of the LR (R) is a function of the transverse tension, being very large at tensions from 2 to 10 grams For this muscle R is always smaller for a given tension when the cathode is some distance away from the stylus Since, at the stylus cathode, the immediate response is purely local and thus free of any transmitted mechanical wave effects, and since the LR precedes contraction at that spot, the LR must represent an intrinsic physiological precontractile elongation of the muscle

In the axial technique, the muscle is vertically oriented in Ringer's solution with its free end connected to the stylus Excitation is affected by large Ag-AgCl band-electrodes symmetrically flanking the muscle Thus all segments of the muscle's length are simultaneously excited and no transmitted mechanical wave exists R is now 3 to 4X that produced by the same muscle excited by wire electrodes, and the increased value of R is attributed to the synchronous activity of the entire muscle length Since an LR is obtained in the absence of any transmitted wave, the LR is attributed to a real precontractile elongation of the excited muscle

The presented evidence thus disproves the theory of Schoepfle and Gilson that the LR is a compression wave artifact Other evidence will show that the LR is a consequence of the activation of myosin for contraction

Cholinesterases in peripheral nerve fibers CHARLES H SAWYER (introduced by J E Markee) *Dept of Anatomy, Duke Univ, Durham, N C* Acetylcholine (ACh) functions at the neuronal surface, and there is considerable evidence that its specific cholinesterase (ChE) in peripheral nerves is secreted by the axis cylinders The results of experiments outlined here confirm that most, but deny that all, of the enzyme is produced by the axis cylinders themselves (1) Relatively large quantities of the specific or true ChE and small amounts of the non specific or pseudo ChE are present in the guinea pig sciatic nerve (2) Sectioning this nerve leads, within the first few days,

to a 60% loss of true ChE from the degenerating tibial and peroneal nerves There is no further loss of this esterase even on complete disintegration of the axons Pseudo ChE activity is unaffected by the operation while the total ACh hydrolyzing capacity, dependent on the two enzymes, decreases 30% (3) Neuromas, developing on the proximal ends of the sectioned sciatic nerves, contain great numbers of fine regenerating axons, and their ACh hydrolyzing power is 3 times as great as that in the controls The rise is due almost entirely, if not totally, to increased true ChE content (4) It is concluded that nearly two thirds of the true ChE in the control nerves is secreted by the axis cylinders, but that more than one third is produced by some other element or elements, perhaps Schwann's sheath cells Pseudo-ChE is probably completely resident in the connective tissue of the sheaths

Reflex activity in the lower extremities after verified transection of the spinal cord in man JOHN E SCARFF and JAMES L POOL (introduced by Fred A Mettler) *Dept of Neurology, College of Physicians and Surgeons, Columbia Univ, New York City* Thirty-three of forty-one paraplegic patients with traumatic lesions of the spinal cord between the 7th cervical segment and the 10th thoracic segment suffered with massive involuntary spasms of the legs Five of these patients with severe spasms of twelve months duration, or longer, were explored at the sites of the lesions In each case the fact of previous complete transection of the spinal cord was established, and the stumps of the previously severed cord which had been, in all instances, densely adherent to the dura were liberated and excised

Prior to our operations, the tendon reflexes in these five patients were generally, though not invariably, exaggerated After operation, there was a marked reduction in the tendon reflexes in four of the five cases

In three of the patients stroking the sole of the foot yielded no response of any sort In one patient there was a vigorous plantar flexion of all toes In three patients there was slight dorsiflexion (extension) of the toes Following operation there were changes in the plantar reflexes which, however, conformed to no fixed pattern The positive Babinski sign did not invariably follow transection of the cord in man It did occur in certain instances but the factors governing its occurrence were not evident Surgical procedures carried out on the distal stump of the divided cord affected the plantar reflexes in various manners

The characteristic pattern of changes in nitrogen metabolism after trauma VICTOR SCHENKER (by invitation), J A F STRIVANSON (by invitation) and J S L BROWN *McGill Univ Clinic, Royal Victoria Hospital, Montreal, Canada* Nitro

gen balance studies have been conducted in 150 subjects. These investigations demonstrate that the nitrogen metabolism of adult patients in good health at the time of injury, undergoes a series of changes which follows a characteristic pattern quite irrespective of the nature of the trauma.

On comparison of the rate of nitrogen elimination in the urine of patients with burns, fractures, muscle-wounds, and after surgical operations, with that of paired-fed, healthy subjects, it is shown that for a time after acute trauma this rate is markedly increased. This 'catabolic response' reaches its maximum intensity within a week or so after the initial injury, then gradually subsides, although secondary stimuli (e.g. infection, surgical operations and manipulations) may prolong its duration by eliciting corresponding secondary responses. This interval has been termed the 'catabolic period'.

These catabolic phenomena merge into a second phase in the metabolism of nitrogen, and there occurs the 'anabolic period' which is characterized in the same individual, by the *retention* of nitrogen, in contrast to the loss of nitrogen which occurred during the 'catabolic period' at the same level of food intake. This anabolic tendency becomes progressively less and less pronounced as the patient recovers his previous healthy state.

Synaptic delay and central inhibition in relation to electrotonic potentials. By GORDON M. SCHOEFFLE, *Physiological Dept., School of Medicine, Washington Univ., St. Louis*. The classical local circuit theory of nerve impulse transmission demands that polyphasic voltage-time relations exist at points in the conducting medium surrounding the fiber. With this in mind voltages were determined at points in a medium of 6.8% sucrose solution surrounding isolated nerves and isolated (but intact) muscles. All potentials are referred to an inert (distant) point in the medium.

A positive deflection precedes the negative component regardless of the local electrode position with respect to the fiber. In fact, a relatively pure positive monophasic deflection may be obtained near the tips of both nerve and muscle fibers. If a membrane discontinuity exists at the synapse a positive or inhibitory potential variation will precede the negative or excitatory variation. Hence an apparent synaptic delay will be manifest if conduction times are determined in the usual manner. This argument is consistent with recent concepts of activation across the A-V junction in heart (Gilson, A. J. P. 138-113, 1942). Electrotonic spread of potential across a block in a single nerve fiber should involve no initial anodal polarization of the membrane beyond the block since there exists no membrane discontinuity (Erlanger, A. J. P. 126-97, 1939). The same considerations may apply to conduction across septal divisions in

earthworm nerve fibers in which case no delay is apparent (Bullock, J. Neurophysiol. 8:55, 1915).

A straight end to end orientation of neurones in synaptic relationship without overlapping would apparently involve inhibition without subsequent excitation.

A comparative study of the methods for resuscitation from carbon monoxide asphyxia. H. SCHWENMA (by invitation), A. C. IYER, A. E. SIEWITZ, JR. (by invitation), W. WOLMAN (by invitation) and H. FRIDMAN (by invitation). *Dept. of Physiology, Northwestern Univ. Medical School, and the Lab. of the American Medical Association, Chicago*. A comparative study has been made of the effectiveness of several commonly used methods of resuscitation in 223 dogs asphyxiated with 0.3 per cent CO.

Dogs were exposed to CO until the first respiratory gasp appeared, and one of the methods was applied. One group was asphyxiated with gas from the city mains, the other with "pure" CO from a cylinder. Manual respiration and mechanical resuscitators of 2 types were used: the E&J (alternating positive and negative pressure) and McKesson (a fixed volume bellows type). Oxygen and 7 per cent carbogen were used in these devices. Two groups of dogs, one exposed to city gas, the other to cylinder CO, were untreated after removal from the chamber. All survivors were observed for 2 weeks for the appearance of neurological sequelae.

The following results were obtained when city gas was used, the per cent surviving being given no treatment, 36 per cent, manual respiration and air, 50 per cent, E&J and oxygen, 67 per cent, E&J and carbogen, 75 per cent. Ten per cent of the survivors developed neurological sequelae. There was no relation between the length of exposure and survival, but the neurological sequelae increased with the length of exposure.

The following results were obtained when the "pure" cylinder CO was used, the per cent surviving being given no treatment, 15 per cent, manual respiration and carbogen, 50 per cent, E&J and carbogen, 50 per cent, E&J and oxygen, 47 per cent, McKesson and carbogen, 40 per cent. Neurological sequelae appeared in 66 per cent of the survivors, with an increase in incidence in those with long exposures. Dogs exposed for a long time had a better chance of survival than those exposed for a short time. The rate of clearance of CO from the blood was followed in 10 dogs in each group.

Renal blood flow and renal clearance during hemorrhagic shock. EWALD E. SELKURT, *Dept. of Physiology, School of Medicine, Western Reserve Univ., Cleveland, O.* Reduction of mean blood pressure in dogs to 60 mm. Hg by standardized hemorrhage causes an immediate decrease in direct renal blood flow (R.B.F.) to 41.5 per cent of the control.

value Renal vascular resistance gradually increases as this level of hypotension is maintained for 90 minutes, resulting in further decrease in R B F Minimal R B F occurs during the subsequent 40 mm Hg period, when it is only 11 per cent of the control During this period, renal vascular resistance is greatest

Upon reinfusion of blood, there is restoration of R B F and mean blood pressure to approximately 75 per cent of the control Simultaneously, renal vascular resistance returns approximately to normal Blood pressure and R B F decrease again terminally, but R B F falls more rapidly, due to increasing renal resistance

During hypotension, there is anuria, and the clearance of p-amino hippuric acid (P A H) and creatinine is therefore zero, even while R B F is appreciable Upon reinfusion of blood, the clearance of P A H and creatinine fails to be restored, resulting in large disparities when compared to direct renal blood flow These discrepancies are thought to be due to renal tubular impairment, created by anoxia during the hemorrhagic hypotension This is evidenced by reduction of the extraction ratio of P A H, and by marked decrease in the U/P of creatinine Histological examination of representative kidneys revealed a diffuse nephrosis, with cloudy swelling and hydropic degeneration of the tubular cells

Beta dimethylamino-ethyl benzhydryl ether hydrochloride as an antihistamine and anti-anaphylactic agent W A SELLE *Dept of Physiology, Medical School, Univ of Texas, Galveston* Detailed studies confirm the observations of Loew et al that B dimethylaminoethyl benzhydryl ether hydrochloride is a potent antihistamine and anti-anaphylactic agent The drug was tested on isolated tissues of normal and sensitized guinea-pigs and on intact normal and sensitized animals One tenth milligram of the drug prevented contraction of the isolated uterus and ileum suspended in 20 cc of Locke's solution to which 10 gamma of histamine was added Using the Schultz-Dale technique, 2 mg prevented the anaphylactic contraction of guinea pig ileum subjected to an assaulting dose of antigen Ten milligrams injected intraperitoneally into 600 gram guinea-pigs protected the animals against 3MLD of histamine The drug was also effective in significantly reducing the incidence of fatal anaphylactic shock in sensitized animals In the latter experiments, intrajugular injections of antigen (egg albumin) were made into sensitized but untreated control animals and into sensitized animals which had received 15 mg of the drug intraperitoneally 30 minutes previously Eight of ten treated animals survived anaphylaxis while only one of ten untreated animals did so The results indicate that the drug is the most potent anti-

histamine and anti anaphylactic compound studied thus far

Effect of the diet upon the renotropic, nephrosclerotic, cardiotropic and adrenotropic actions of crude anterior pituitary preparations By HANS SELYE and HELEN STONE (by invitation) *Inst of Experimental Medicine and Surgery, Univ of Montreal, Montreal, Canada* "Acidifying salts" (NH_4Cl , CaCl_2 , etc) or large amounts of carbohydrate (glucose, starch) counteract the nephrosclerosis producing and kidney enlarging (renotropic) effects of anterior pituitary preparations This has now been confirmed with a variety of simple, natural diets Rats, sensitized to the nephrosclerotic action of lyophilized anterior pituitary (LAP) by unilateral nephrectomy and the substitution of 1% NaCl for drinking water, were fed exclusively on skeletal muscle, cardiac muscle, "purina" fox chow, peas, lentils, corn, lima beans or rice Each diet was given to a group of 20 rats (average initial body weight, 83 grams), half of the animals receiving, during 17 days, daily subcutaneous injections of 20 mg of LAP, the other half (controls) the same amount of lyophilized liver extract The average renal, heart and adrenal weights of the LAP treated groups decreased in the order in which the diets are enumerated above The degree of nephrosclerosis and the final organ weights were closely proportional to the protein (and inversely proportional to the carbohydrate) content of the diets in all groups

The liver extract failed to cause any significant organ changes on any of the diets

It is concluded that the ability of anterior pituitary preparations to cause nephrosclerosis and renal, cardiac and adreno-cortical enlargement is largely dependent upon the protein content of the diet and counteracted by carbohydrates This confirms earlier observations made in this laboratory under slightly different experimental conditions and shows the importance of the diet in evaluating bioassays for the above mentioned pituitary activities [Aided by a grant of the Commonwealth Foundation]

The action of sulfanilamide on the resting potential of frog nerve A M SHANES (introduced by D E S Brown) *Dept of Physiology, New York Univ College of Dentistry* The highly mobile hydrogen ion, arising by virtue of tissue CO_2 production and its subsequent conversion to carbonic acid, has been suggested as a possible source of bioelectrical potentials The efficacy of such a process might well be dependent upon the catalysis of the reaction $\text{H}_2\text{O} + \text{CO}_2 \rightleftharpoons \text{H}_2\text{CO}_3$ by carbonic anhydrase

Sulfanilamide, purported to be a specific inhibitor of carbonic anhydrase, has been applied in concentrations of 100 mg % to frog sciatic nerve as a test of the involvement of this enzyme No

appreciable effect on the resting potential has been observed in oxygen after 2 or 16 hours of soaking in this inhibitor. However, during 2 hours of anoxia, the decrement of potential is only 0.6 that of the controls, while the increment upon return to oxygen is smaller still. P amino benzoate produces neither effect, nor does it counteract sulfanilamide, these negative results are consistent with the possibility that sulfanilamide is inhibiting carbonic anhydrase. Furthermore, the action of sulfanilamide on the decline of potential in nitrogen as well as on the recovery in oxygen can be interpreted readily in terms of such inhibition. The system catalyzed by carbonic anhydrase is therefore believed to be one likely mechanism in the production of resting potentials.

The effects of smoking on the dark adaptation of rods and cones CHARLES SHERR, *Division of Physics and Biophysical Research, Mayo Foundation and Mayo Clinic, Rochester, Minnesota*. A series of investigations was made on several subjects regarding the effects of smoking cigarettes on the levels of dark adaptation, with controlled conditions and specified criteria, under the following circumstances: (1) inhaling smoke, (2) smoking but not inhaling, (3) inhaling smoke drawn through filters absorbing nicotine, (4) smoking cubebs, corn-silk cigarettes and other materials which did not contain nicotine and (5) breathing pure oxygen prior to and during all adaptation tests in each of the foregoing procedures.

These investigations show that (1) there is a definite decrease of level of light sensitivity (0.25 to 0.75 log unit) in both rods and cones which persist for 15 to 30 minutes after inhaling smoke from two standard cigarettes, (2) the effects are practically the same if the smoke is drawn into the mouth and not inhaled, (3) there is no effect on the adaptation levels when the nicotine is removed (that is, less than 5 per cent remains) from the smoke by suitable filters, (4) the responses of cones are less affected and the recovery is more rapid than for the rods, (5) the breathing of pure oxygen instead of air has little if any effect on the rate or total time of recovery to previously established levels, and (6) there is no effect of smoking cubebs, corn-silk cigarettes and similar types of material containing no nicotine. These findings show that the smoking of standard cigarettes reduces, and therefore acts adversely for 15 to 30 minutes on, the dark adaptation levels of both rods and cones, owing largely if not wholly to nicotine.

Acclimatization of men to high temperatures WALTER B. SHELLEY,¹ (by invitation) and STEVEN M. HORVATH,² *Armored Medical Research Lab, Fort Knox, Kentucky*. Acclimatization to moderate

levels of environmental heat has been studied extensively, but little is known regarding the physiological adjustments occurring in men working at very high temperatures. Previous experience has indicated that the amount of work that can be performed by clothed men at an environment of D.B. 120°F and W.B. 92°F is very small.

Sixteen young soldiers, after two weeks of preliminary training, started work, walking at 2.9 mph (250 Cal/Hr) in an environment of 120°F–93°F. They were dressed in herringbone twill uniforms. On their first exposure they walked for 0.5 hours. On each succeeding day they walked a full hour in the heat and their acclimatization to this amount of work was studied. The following table presents data obtained at the end of the hour on the second and fourteenth day in the heat. Acclimatization at "upper limits" follows the pattern observed in exposures to milder environmental heat loads.

	Rectal temp, °F	Pulse rate per min	Final mean skin temp, °F	Weight loss gm/hr
	Mean	Mean	Mean	Mean
2nd day	104.2	162	101.8	1556
14th day	102.8	149	100.1	1882

The average amount of work that could be performed at this environment on the first day of exposure was 0.5 hours while after two weeks of work these men were able to walk on the average 1.6 hours, with two men walking for 2.4 hours.

In an attempt to determine the degree to which acclimatization to an extremely hot environment would influence performance at lower environments, twelve of these men then walked at both 120°F–90°F and 120°F–88°F. All subjects walked the four hours required. However, it appeared that these men, acclimatized to one hour of work at 120°F–93°F, were only partially acclimatized to four hours of work at 120°F–90°F, but were fully acclimatized to four hours of work at 120°F–88°F, as evidenced by additional exposure to these environments.

Age changes in kidney function of human subjects NATHAN W. SHOCK, *Division of Physiology, National Inst. of Health, Bethesda, Md. and Baltimore City Hospitals, Baltimore, Md.* Kidney function was measured in a group of 50 colored males, aged 20–80 years who were free from clinical signs or previous history of cardiovascular or renal disease. The following tests were applied to each subject: concentrating ability, urea clearance, inulin clearance, diodrast clearance, diodrast T_m , and rate of excretion of orally administered acid and alkali.

¹ Captain MC, AUS

² Major SnC, AUS

Concentration capacity of the kidney showed the least diminution with age. Urea and inulin clearances showed a gradual decrease after the age of 50 years. Tubular function, as measured by diodrast clearance and rate of excretion of acid and alkali, showed some reduction as early as 40 years of age. The extent of impairment was greater for tubular function than for glomerular filtration at the higher age levels. Average values for both tubular and glomerular function diminished gradually with increasing age. Diodrast T_m also diminished gradually at ages greater than 40 years. Some 70 year old subjects showed kidney function equal to that of 20 year olds.

Cortical autonomic center for the eyes on the mesial surface of the frontal lobe in cat. ARTHUR A. SIEBENS (by invitation) and CLINTON N. WOOLSEY, *Dept of Physiology, Johns Hopkins Univ, School of Medicine, Baltimore, 5, Md.* Cortex on the mesial surface of one hemisphere was exposed and stimulated at 2 mm intervals with 60 cycle current or Harvard inductorium under pentobarbital anesthesia. The region from which autonomic effects were produced lies above the level of the corpus callosum and anterior to the cruciate sulcus, reaching nearly to the rostral pole of the hemisphere. It extends only slightly onto the dorsal surface of gyrus proreus. The area yielding maximal effects is centered about 4 mm below the dorsal edge of the hemisphere and approximately 3 mm rostral to the point where cruciate sulcus and sagittal sinus meet.

Effects produced were bilateral. From the center of the area wide dilatation of pupil, complete retraction of nictitating membrane and marked exophthalmos were elicited. From peripheral parts of the area smaller responses were obtained. In some animals all three effects occurred together, in others only dilatation of the pupil. Dissociation by anesthesia indicates that the cortical system need not act equally on all effectors.

After section of one cervical sympathetic the pupil of that side still dilated on cortical excitation (parasympathetic inhibition), but the effect was small compared with the response before section. On the other hand, the pupil still actively dilated when only the oculomotor nerve was cut unilaterally. Thus the cortex evoked reciprocal actions in the sympathetic and parasympathetic innervations of the pupil. Our results differ from previous observations as regards both the locus of the cortical area and the mechanism of dilatation.

Degenerative changes induced in the C.N.S. of albino rats by exposure to O₂ at high pressure. (Read by title) ERNEST C. SIEGFRIED (by invitation) and JOHN W. BEEAN, *Dept of Physiology, Univ of Mich, Ann Arbor.* Albino rats were exposed to O₂ at increased pressure (usually 65 pounds

gauge) for short periods of from 10 to 25 minutes 2 to 4 times per day over such periods of time as to induce definite permanent motor dysfunction, because of wide variation in individual susceptibility the program of exposures varied considerably for different animals. Decompression was such as to preclude the possibility of bubble formation. Following the last exposure an interval of about 14 days was provided to permit degenerative changes, which may have been induced, to become demonstrable histologically. The animals were then sacrificed and brain and cord prepared for serially sectioning and stained (Weigert).

Histological examination revealed numerous sites of degenerative changes varying in degree from slight to very severe. The most common and prominent degeneration was found in the cortico spinal tract, less pronounced and less constantly, degenerative involvement was found in the fasciculus gracilis, and the dorsal cerebellar tracts, the brachium pontis, cerebral peduncles, and corpus callosum. In a few preparations there was some evidence of an involvement of the optic nerve. The severity and extent of the histopathology was not uniformly commensurate with the severity and extent of the motor dysfunction manifest by the animal prior to its sacrifice. The results indicate a wide spread deleterious effect of O₂ at these pressures on the C.N.S. and extend and confirm earlier findings previously by one of us (*J. W. B. Physiol. Rev.*, 25, 1, 1945) m.

Electrocardiographic changes in semi-starvation. ERNEST SIMONSON, *Laby of Physiological Hygiene, Univ of Minnesota.* Electrocardiograms (3 standard leads) were taken on 32 subjects in the basal state before and after 12 and 24 weeks of semi-starvation which produced an average weight loss of 25%. The electrocardiograms became definitely abnormal in 25 subjects. Only the P-R interval, QRS interval, and the ST segment remained relatively unaffected. At the end of semi starvation the average heart rate had dropped from 54.7 beats per minute to 37.2, associated with a narrowing of the range of cycle variability from 14.7 to 8.8 per cent. Sinus arrhythmia disappeared completely. The QT interval lengthened in proportion to the RR interval, so that $K_{QT} (= QT/(RR)^{1/2})$ remained constant. The mechanical systole duration (measured from the electrophonogram) increased proportionally less than the RR interval, so that K_{me} became smaller. The amplitudes of the P wave, QRS complex and T wave decreased and at the end of semi starvation were approximately half their original size. While the interval changes attained their maxima by the 12th week of semi-starvation, the voltage changes were either constantly progressive (P wave, QRS complex) or changed only after 12 weeks (T, T). Although the

voltages of all waves decreased in semi starvation, the extent of the changes in the several waves showed little correlation. Both the QRS axis and the T axis shifted to the right, this change being more pronounced in the T axis, so that the angle between both axes was reduced, indicating a changed direction of the repolarization. All changes were highly significant. *[This work was supported in part under a contract with the Office of Scientific Research and Development. Support from other sources will be acknowledged in final publication.]*

Maximum speed of movement as a test of muscle function in different nutritional states. ERNEST SIMONSON and JOSEF BROZIK (by invitation) *Laby of Physiological Hygiene, Univ of Minnesota, Minneapolis, Minnesota* (Read by title) Electrical devices to measure the speed of a quick knee kick over an angle of 45° without and with load (10 pounds) were developed. Satisfactory repeatability and relative freedom from training effects were demonstrated. Correlation of speed with strength (dynamometer) was absent in a group of normal individuals and was imperfect within the individual in different states of fitness and debility. In 12 normal young men the time for the complete motion averaged 101.8 milliseconds (76 to 115) without load and 114.3 (85 to 123) with load. Fourteen days of acute thiamine deficiency produced statistically significant increases of time with and without load (averages $+7.21$ and $+9.72$ msec, respectively). After 6 months of semi-starvation (to 75% of original weight) 32 young men averaged 130.2 msec (110-165) without load and 164.8 (133 to 227) with load. The values of this group were significantly different from those of the group of 12 normal men. During the 42 days of nutritional rehabilitation 16 of these men receiving 2200 and 2600 Cal daily showed no improvement without load, and with load these men showed a small improvement (-10 msec). In the same period the 16 men receiving 3000 and 3400 Cal improved significantly both without load (-6.3 msec) and with load (-19.7 msec). *[This work was supported in part under a contract with the Office of Scientific Research and Development. Support from other sources will be acknowledged in final publication.]*

Interplay of half-centers. JEANE SISKEL (by invitation), E. T. HANSEN (by invitation) and ROBERT GESELL *Univ of Michigan*. Dominant stimulation of the inspiratory half-center, by application of faradic shocks of moderate intensity to Hering's nerve, increased the duration and strength of inspiration. Stimulation of the superior laryngeal nerve in the course of such augmented inspirations suddenly interrupted the contractions of inspiratory muscles and initiated the expiratory phase of breathing. Interruption of these inspira-

tory contractions is, presumably, the result of reciprocal inhibition of the inspiratory half-center originating in the reflex activation of the expiratory half-center. Strong stimulation of Hering's nerve was found to increase the strength of both inspiration and expiration and to shorten the period of inspiration. This earlier interruption of the inspiratory act is partly attributed to the augmented activity of the expiratory half-center and a consequently earlier reciprocal inhibition of the inspiratory half-center.

The relative activation of the inspiratory and expiratory half-centers produced by stimulation of Hering's nerve seemed to vary from one animal to another. Though decidedly more inspiratory than expiratory in most animals, Hering's nerve was occasionally found to be predominantly expiratory. Such dominance tended to produce early interruption of the inspiratory act.

In one animal with expiratory dominance, intravenous injection of urethane depressed the reflex response of the expiratory half-center to Hering nerve stimulation more than that of the inspiratory half-center, thus changing breathing from a distinctly expiratory to a distinctly inspiratory type. Such drug action acquires greater interest if an interplay of half-centers exists in the higher integrations as well as in the simpler motor integrations.

The action of tyrosinase on proteins. IRWIN W. SIZER *Dept of Biology, Mass Inst of Technology, Cambridge*. Both crude and highly purified mushroom tyrosinase has been demonstrated to oxidize the tyrosyl groups of such proteins as trypsin, pepsin, chymotrypsin, casein, peptone, insulin, and hemoglobin. It did not oxidize gelatin, protamine and gramicidin which do not contain tyrosine. Certain proteins containing tyrosine were resistant to tyrosinase, these included egg albumin, human and bovine serum albumin, tobacco mosaic virus, human gamma globulin, bovine beta globulin and bovine fibrinogen. All of this group, which were studied, were oxidized by tyrosinase after a preliminary treatment with crystalline trypsin.

Several techniques were employed in studying the action of tyrosinase on proteins all of which methods yielded consistent data, these procedures included 1 the measurement of oxidation manometrically from oxygen consumption, 2 the measurement of phenolic groups using Millon's test on intact proteins, 3 the quantitative determination of tyrosine in protein hydrolysates, 4 the quantitative measurement of pigment production in the blue-violet caused by the action of tyrosinase on proteins, 5 the measurement of change in the ultraviolet absorption spectrum especially at $275\text{ m}\mu$ at which wave-length the protein absorption is due to tyrosine and tryptophane.

In contrast to most chemical reagents which react with the tyrosyl groups to destroy the biological activity of the protein, tyrosinase has no effect on the enzymatic activity of pepsin, trypsin, and chymotrypsin. This difference may reflect the fact that oxidation of proteins by tyrosinase is less extensive than by chemical agents.

Adrenal function following ovariectomy in the rat DOUGLAS E SMITH (introduced by F A Hartman) *Dept of Physiology, The Ohio State Univ, Columbus* Studies on sodium metabolism and glyconeogenesis, processes known to be largely under the influence of the adrenal, were made at various times after ovariectomy of the sexually mature albino rat. The effects of the operation on adrenal weight and on adrenal cholesterol and sudanophilic material were also determined. At 10 days after operation, no changes were found in any of the factors studied, but from the 56th to the 245th (longest interval in these experiments) post-operative day it was observed that the plasma sodium level was significantly increased, the amount of glyconeogenesis by the liver during fasting was about 2X normal, the adrenal weight was possibly slightly decreased and the cholesterol and sudanophilic material of the adrenal cortex were decreased. These changes were considered to indicate that there is an increased secretory activity of the adrenal cortex following ovariectomy. It is suggested that the increased secretory activity of the adrenal might be due to an increased secretion of adrenotrophic factor by the anterior pituitary.

The effect of sympathectomy and tilting on arterial blood pressure, cardiac output and right atrial pressure in man EDWIN L SMITH (by invitation), B W HAYNES (by invitation), and E I EVANS *Depts of Physiology and Surgery, Medical College of Virginia, Richmond* Cardiac output, femoral arterial blood pressure and right atrial blood pressure have been studied in a series of six hypertensive subjects before and after sympathectomy by the Smithwick technique. A third series of observations has also been made on the sympathectomized patients after tilting them feet down at a 30° angle.

Sympathectomy produced an average drop in mean femoral blood pressure of 22 mm of Hg. The values ranged from a drop of 50 mm Hg to an increase of 20 mm Hg. Tilting caused an additional average drop of 18 mm Hg.

The average cardiac output was 3.2 liters per square meter body surface area before sympathectomy, 3.6 after sympathectomy and 3.8 when tilted. These changes are not considered significant.

The right atrial pressure dropped an average of 2.1 cm of saline for the six cases following sympathectomy but was not altered by tilting. [W or]

done under contract with Office of Scientific Research and Development]

The protective action of cystine and methionine in rats exposed to methyl chloride WILLIE W SMITH *Industrial Hygiene Research Lab, National Inst of Health, Bethesda, Md* Weanling, male, litter-mate rats in groups of 10, after a preliminary period of 2 weeks on the specified diets, were exposed to methyl chloride 2000 p.p.m., 6 hours a day, 6 days a week, until death, diets being continued throughout the exposure period. Mean survival time with a 9% casein diet was 8 days, 20% casein 11 days, 25% casein 17 days, 35% casein 30 days, 47% casein 26 days, and 60% casein 23 days.

When half of the amino nitrogen is in the form of the casein hydrolysate, amigen, with cystine and methionine contents balanced, survival is lengthened to 20 days at the level of 20% and 36 days at 47%.

If, instead of amigen, only cystine and methionine are used, when these amino acids are equivalent to their content in the 20% casein diet the mean survival time increases to 40 days, and to about 80 days when the diet contains 20% casein, 0.143% cystine, and 0.945% methionine (equivalent to the 47% casein diet). The protective action is also demonstrated in better growth rates during exposures.

Unprotected rats usually die before the development of a neurological syndrome which the supplemented groups show late in the course of exposures.

The protective action of the amino acids appears to be dependent upon potential sulfhydryl content which is not entirely available from protein. The mechanism of this action is now under investigation.

The effect of pentobarbital sodium upon the resistance to asphyxia in the newborn FRANKLIN F SANDER *Depts of Anatomy and of Obstetrics Harvard Univ* (Read by title) In observations upon the rôle of anesthetic agents in asphyxia of the newborn, the effect of pentobarbital sodium was investigated in a series of rabbits at various stages of development, ranging from animals prematurely delivered at the time of onset of viability, to those obtained during early postnatal and adult life. In a group of 55 animals obtained from 25 litters pentobarbital sodium was injected subcutaneously in a dosage of 20 mg per kg. Within one hour following injection, asphyxia was induced by ligation of the trachea. The duration of respiratory movements following tracheal ligation was determined by aid of kymograph records using a plethysmograph attached to a recording tambour.

Observations showed that following pentobarbital sodium the duration of respiratory movements was not shortened, but rather was prolonged,

for instance, they persisted for 72 minutes in premature rabbits born at 30 days. In contrast, in non-injected controls of the same age respiratory movements ceased at 55 minutes following obstruction of respiratory exchange. This result is even more striking when the baseline is represented by the average survival time of animals succumbing to oxygen deprivation by breathing nitrogen instead of air, in which case respiratory movements cease at 41 minutes, in rabbits at 30 days. It is of interest that the response to asphyxia, as expressed in terms of the survival time of the animal, was found to be within reach of experimental modification, and especially that the duration of respiration was prolonged [Supported by a grant from the John and Mary R. Markle Foundation].

Accuracy of indirect determinations of blood pressure in the rat relation to temperature of the plethysmograph and width of cuff S. S. SONN (introduced by E. M. Landis) *Dept. of Physiology, Harvard Medical School, Boston, Mass.* The indirect plethysmographic method of measuring systolic blood pressure in the rat's tail has still been found unreliable despite the use of recently recommended modifications of technique. Preliminary study indicated that the inaccuracy of the method arose in part from persisting vasoconstriction in the tail. Warming the tail and plethysmograph to 43°C dilated the caudal artery, produced clear arterial pulsations in the capillary tube of the plethysmograph, made the end-point more precise, and markedly improved the accuracy of the method. The temperature and time for release of caudal vasoconstrictor tone were quite critical.

To measure the effect of release of caudal vasoconstrictor tone on the accuracy of the indirect method, systolic blood pressures were measured simultaneously (a) directly in the femoral artery (Hamilton manometer) and (b) indirectly in the caudal artery, with the plethysmograph at 20°C and 43°C, using 10 and 40 mm occlusive cuffs. With the 10 mm cuff and cool plethysmograph the error of the indirect method was -21%, warming the plethysmograph eliminated this error. With the 40 mm cuff and cool plethysmograph the error of the indirect method was -27%, warming did not eliminate error but merely reduced it to -5.8%.

Falsely low indirect pressures with a narrow occlusive cuff away from the base of the tail, and the error of the wide cuff even when the tail was adequately warmed, suggested the existence of a pressure gradient along the caudal artery. Mean blood pressures in the caudal artery at different levels measured by the micro-injection technique, compared to mean pressures in the carotid artery measured simultaneously, demonstrated such a pressure gradient which amounted to about 4%

per cm in the proximal two thirds of the dilated caudal artery.

Fixed persistence in the rat of spinal reflex patterns rendered extremely maladaptive by cross union of sensory nerves (motion picture) R. W. SPRUNT *Harvard Univ., Cambridge, Mass.* Nerves of the left hind foot were transected and crossed contralaterally to the peripheral stumps of the corresponding nerves of the right foot, so that after nerve regeneration the right foot was reinnervated only by nerves that originally had supplied the left foot. This led in all cases to erroneous contralateral localization of stimuli applied to the reinnervated foot and also to a reversal of hind limb reflexes initiated through the crossed sensory nerves. Although extremely maladaptive, the reversed reflex reactions nevertheless persisted without inhibition or correction by central nervous readjustment. A full printed account of the experiments is reported in *J. Comp. Neur.*, vol. 78, pp. 59-90.

Influence of the superior colliculus upon the vestibulo-ocular reflex E. A. SPIEGEL and N. P. SCALA (by invitation) *Dept. of Exp. Neurology, Temple Univ. School of Medicine, Philadelphia, Pa.* A comparison of the effect of unilateral section of the optic tract upon postrotatory nystagmus (Spiegel and Scala, *Fed. Proc.* 4:67, 1945) with that of unilateral occipital lobectomy (Wycis and Spiegel, *Fed. Proc.* 4:79, 1945) showed in cats that the directional preponderance of postrotatory nystagmus toward the lesion lasts much longer and is more intense after tractus lesion than after ablation of the area striata. These observations suggested that retinal impulses inhibiting the vestibulo-ocular reflex are taken their way not only over the area striata, but also over a subcortical pathway. Unilateral lesions were therefore placed in the anterior corpora quadrigemina in cats, injury to the occipital lobe being avoided as much as possible. Rotation on an electrically driven Bárány chair before and after operation showed that the lesion of one anterior corpus quadrigeminum was followed by a definite increase of the postrotatory nystagmus to the side of the lesion. The same effect of such a lesion appeared, when first a unilateral occipital lobectomy was performed, and the lesion of the homolateral superior colliculus was produced in a second operation, after the directional preponderance produced by the occipital lobectomy had subsided. It is inferred from these experiments that the anterior quadrigeminal body is intercalated in a subcortical pathway originating in the retina and carrying inhibitory impulses to parts of the vestibulo-ocular reflex arc concerned with postrotatory nystagmus to the respective side.

Loss of righting reflexes in experimental cerebral concussion E. SPIEGEL and M. SPIEGEL-

ADOLF (by invitation) *Depts of Exp Neurology and Colloid Chemistry, Temple Univ School of Medicine, Philadelphia* (Read by title) In acceleration concussion produced by the blow of a pendulum to the freely movable head, one of the most striking signs observed in guinea pigs and cats is the animal's inability to right the head from a side or hanging position into the normal position. The disturbance of righting outlasts the loss of the corneal reflex and apnea for from ten minutes to several hours. It is often more pronounced in one side position than in the other, so that it cannot be simply attributed to general exhaustion, it also appears independently of anesthesia. It may be associated with signs of labyrinthine impairment such as disturbances in the appearance of post-rotatory nystagmus, but may be more prolonged than these latter signs. Lesion of the peripheral labyrinth as assumed by Govons, Lewey and Grant in blast injuries, may play a contributory rôle. However, there is a transient loss not only of labyrinthine, but also of body righting reflexes, in cats also of optical righting reflexes, the inability to right the head being found not only when the animal is held in the air, but also if it lies on its side on the ground.

Apparently one deals with a chiefly central, rather diffuse disturbance involving the mesencephalon in the case of the labyrinthine and body righting reflexes and the cerebral cortex in the case of the optical righting reflexes. [Aided by a grant from the John and Mary R. Merkle Foundation.]

The inhibition of enzyme formation. S. SPIEGELMAN (introduced by H. B. Steinbach) *Dept of Bacteriology, Washington Univ School of Medicine, St. Louis, Mo* (Read by title) The incubation of non-dividing suspensions of *S. cerevisiae* in the presence of excess galactose induces the synthesis of the enzyme system necessary for its fermentation. This phenomenon has been used to study the physiology of enzyme formation. It has been established that energy derived from either respiratory or fermentative metabolism may be used for enzyme synthesis although the former is more effective. Interference with the overall metabolism invariably results in the cessation of enzyme formation.

10^{-2} M NaN_3 (as well as higher concentrations) completely prevents anaerobic formation of enzyme although stimulating the rate of utilization of the fermentable substrate supplied. If less than maximal enzyme is allowed to form first and then azide is introduced, no further enzyme synthesis occurs. Removal of substrate after enzyme formation results in disappearance of the enzyme from the cell at a rate proportional to metabolic turnover. Such loss of enzyme can be prevented by halting cellular metabolism. NaN_3 , however, can prevent such dis-

appearance of enzyme even in cells metabolizing at maximal rate. This would imply a close connection between enzyme formation and breakdown.

The ability of NaN_3 to prevent utilization of metabolic energy for synthesis is quite general having been demonstrated for such diverse processes as cell division, carbohydrate and ammonia assimilation, embryonic development, and regeneration. Dinitrophenol was also found to prevent anaerobic enzyme synthesis. Cyanide was however ineffective.

The site of uncoupling of phosphorylation from carbohydrate metabolism in the presence of NaN_3 . S. SPIEGELMAN and M. D. KAMEN (introduced by H. B. Steinbach) *Dept of Bacteriology and the Mallinckrodt Inst of Radiology, Washington Univ School of Medicine, St. Louis, Mo*. Our previous experiments with P^{32} showed that NaN_3 could drastically reduce phosphate turnover in yeast cells metabolizing sugar at normal rates. According to the classical glycolytic mechanism the equilibration of inorganic P with the organic P of the cell occurs by the entrance of inorganic P into the carbohydrate cycle in two places: (1) phosphorylation of glycogen, (2) the coupled oxidation and phosphorylation of glyceraldehyde P to di-P-glyceric acid.

Since it seemed most probable that the azide was affecting step (2) experiments were devised to examine the behaviour of the fermentative cycle at this level in the presence of azide. It is well known that IAA is a strong inhibitor of the enzyme (glyceraldehyde oxidase) controlling this step. It was reasoned that if azide modified the phosphorylative mechanism at this step it might be expected that a parallel change in the sensitivity of the fermentation to IAA would appear, and such was found. A concentration of IAA (2×10^{-4} M) which was sufficient to inhibit fermentation completely within 10 minutes in the absence of azide, took 180 minutes to bring the rate down to zero in the presence of 5×10^{-3} M NaN_3 , and failed to affect the rate at all for the first 70 minutes. Lower concentrations of azide protected against IAA inhibition to a lesser extent. Higher concentrations continued to lengthen the period of protection until inhibitory concentrations of azide were reached, whereupon the protective action against IAA disappeared. It was further found that no concentration of azide could reverse the IAA inhibition once it was established nor was it at all effective against fluoride inhibition of fermentation.

These results are consistent with the hypothesis that the azide disassociation of phosphorylation from carbohydrate fermentation occurs at the step catalyzed by glyceraldehyde oxidase.

Mechanism of azide inhibition of synthetic activity and its relation to phosphorylation. S.

SPIEGELMAN, M D KAMEN, and REBA DUNN (introduced by H B Steinbach) *Dept of Bacteriology and the Mallinckrodt Inst of Radiology, Washington Univ School of Medicine, St Louis, Mo* (Read by title) NaN_3 in concentrations which do not noticeably influence respiratory activity can inhibit such diverse synthetic processes as cell division, carbohydrate and NH_3 assimilation, embryonic development, regeneration, and enzyme formation

On the assumption that P-bond energy as generated by the glycolytic system forms the primary source of energy for cell function and growth, experiments were undertaken to examine the effect of NaN_3 on phosphorous metabolism using P^{32} as a tracer All the experiments were done under anaerobic conditions with yeast cells fermenting glucose The time of the experiments was sufficient to allow 100 per cent turnover of the acid soluble P and 35 per cent of the residue P in the controls In the presence of $5 \times 10^{-3} \text{ M NaN}_3$, which permits a fermentation rate 85 per cent of normal, the P turnovers were 2 per cent and 0.7 per cent in the acid soluble and residue fractions respectively 10^{-3} M , which stimulated fermentation about 15 per cent, reduced the P turnover in the two fractions to 10 per cent of normal Barium fractionations of the acid soluble P were made and found not to differ appreciably from one another in their exchange values Total phosphate determinations performed during the course of these experiments confirmed the findings obtained with radioactive P Phosphate accumulation did not occur in those concentrations of NaN_3 which markedly depressed P turnover

These results would suggest that the capacity of NaN_3 to prevent cellular utilization of metabolic energy for synthetic purposes resides in its ability to dissociate carbohydrate metabolism from the generation of energy rich phosphate bonds They would also imply that all the different synthetic processes mentioned above as being inhibited by azide depend on P-bond energy for their accomplishment

Abnormal forms of the ballistocardiogram ISAAC STARR *Univ of Pennsylvania* The relation of the ballistocardiogram to cardiac output was the subject of a symposium of the American Physiological Society last year This report is concerned with another aspect of our work, the study of abnormal forms of the impacts Due to preoccupation with war-time research, it has been difficult to experiment, but the empirical study has now been going on for 10 years and certain conclusions can be drawn from it

Abnormal forms are found most commonly in the older age groups They often occur in the smaller complexes of the respiratory cycle while the larger

remain normal They are usually, but by no means always, associated with other clinical evidence of heart disease They appear frequently after an elderly person has been subjected to a severe operation and usually disappear when he recovers (Starr and Mayo) Abnormal forms have been produced experimentally by a procedure which diminishes venous return (Starr and Friedland)

The relation to the electrocardiogram varies In some cases in which the electrocardiogram shows both normal and abnormal beats, these changes are accompanied by similar variations in the ballistocardiogram In other cases, severe electrocardiographic abnormalities are not accompanied by ballistocardiographic abnormalities, and the reverse is also true The electrocardiogram and the ballistocardiogram give evidence of two aspects of cardiac function not necessarily associated, the former detecting localized lesions better than the latter But the electrocardiogram is little, if at all, affected by major changes in the strength of the heart's contraction which effect the ballistocardiogram profoundly, so the latter gives superior information concerning cardiac strength or weakness

The action of adrenaline and acetylcholine on partially isolated neurones of the central nervous system GEORGE W STAVRAKY *Dept of Physiology, Univ of Western Ontario Medical School, London, Canada* It was shown both in experimental animals and in human beings (Stavraky, G W, *Trans Roy Soc Canada*, 37: 127, 1943; Fisher, S M and Stavraky, G W, *Am J Med Sci* 208: 371, 1944) that aseptic removal of various portions of the cerebral hemispheres results in a lasting sensitization of some remaining parts of the central nervous system to injections of acetylcholine and acetyl-beta-metholcholine

It is now found that intravenous injections of adrenaline into unanaesthetized, semidecerebrated or frontal-lobectomized cats lead to asymmetrical responses which resemble somewhat those elicited by acetylcholine Quantities of adrenaline under 0.03 mg per Kg cause a predominant dilatation of the contralateral pupil and some extensor rigidity in the contralateral extremities Injections of 0.03 mg of adrenaline per Kg have the same effect on the pupils, but cause initial flexion and weakness of the contralateral forelimb which in 45-60 seconds is superseded by extensor rigidity Injections of 0.1 mg of adrenaline per Kg produce at first, a more marked dilatation of the ipsilateral pupil and flexion and weakness of the contralateral extremities These effects last about 2-4 minutes and are followed by a 2-4 minute phase during which the contralateral pupil is wider than the ipsilateral one and the contralateral extremities show extensor hypertonicity

In cats in which facilitation of responses is produced by repeated injections of acetylcholine,

adrenaline causes quick thrusts of the contralateral forelimb and asymmetrical convulsions similar to those produced by acetylcholine. When injected in appropriate amounts, with or before acetylcholine, adrenaline counteracts the initial generalized convulsions evoked by acetylcholine, accentuating the secondary asymmetric motor manifestations produced by this agent. In large quantities, adrenaline counteracts both effects of acetylcholine.

Observations on the synergistic effects of various antispasmodic compounds and nembutal on colon activity in normal adult males. F. R. STEGGERDA, R. K. RICHARDS, and JUSTIN HOEKSTRA (by invitation). *Dept. of Physiology, Univ. of Illinois, Urbana, Illinois, and Dept. of Pharmacology, Abbott Lab., North Chicago, Illinois.* Into adult male subjects who had recently defecated and had had a light breakfast two hours previous to the time of the experiment, an improvised open tipped catheter tube was inserted four to five inches beyond the anal sphincter. Then by injecting 500 to 900 cc. of air into the lower colon via the tube and making connections with a water manometer a series of continuous contractions from the distended colon could be recorded on a smoked drum. By oral administration of an antispasmodic compound, either with or without the addition of Nembutal, the time of onset and duration of the inhibition of colonic activity could be recorded.

The tracings indicate that when a dose of 100 mg. of Amethone (A. P. 43) is taken orally, there occurs an inhibition of colonic activity in approximately 30 minutes, lasting for about 40 minutes. However, when 25 mg. of Nembutal are taken simultaneously with the antispasmodic compound, the period of inhibition lasts at least 50 per cent longer. That this prolonged inhibitory effect, following the administration of the two drugs, is synergistic in nature is supported by the fact that when Nembutal is taken alone, there is no evidence of any inhibition taking place.

Evidence is also available to support the conclusion that Pavatrine acts similarly to Amethone with Nembutal, whereas other experiments indicate that Trasentine and Syntropan do not show a synergistic effect with Nembutal.

The two basic mechanisms of sensory discrimination. S. S. STEVENS. *Harvard Univ.* The hypothesis is proposed that sensory discrimination is mediated by two processes distinguishable at the physiological level: the one *additive*, the other *substitutive*. Excitation may be added to excitation already present, or new excitation may be substituted for excitation that has been removed. Example: we hear loudness differences when to neural units already excited there are added newly activated elements, we hear pitch differences when in place of units previously active there are sub-

stituted units newly excited. Different sets of general laws govern the two types of sensory discriminations. (1) In terms of their subjective magnitude, just noticeable differences (jnd) are unequal when the physiological process is additive, equal when the process is substitutive. In other words, the subjective scale for perceived loudness cannot be obtained by adding up jnd , whereas the integrated jnd for pitch agree closely with the scale for subjective pitch. (2) Discriminations based on additive processes show a systematic "time-error," i.e. the apparent magnitude of the difference varies with the time interval separating the two stimuli, but the time-error is absent when the underlying process is neural substitution. Thus there is a time-error in judgments of loudness, but not in the discrimination of pitch.

The effect of various degrees of intermittent anoxia on body weight loss in normal rats. J. CLIFFORD STICKNEY. *Dept. of Physiology, School of Medicine, West Virginia Univ., Morgantown.* Six adult rats were exposed for $3\frac{1}{2}$ hr. twice weekly to various simulated altitudes (0, 4000, 8000, 14,000, 18,000 ft.) by means of a low pressure chamber. Body weight losses were determined by weighing the rats immediately before and after each experiment. The rats were placed in individual metabolism cages so that urine and feces could be collected and weighed separately. The temperature and relative humidity within the low pressure chamber were recorded for each experiment.

The average body weight loss for 16 control determinations was 13.9 mg./grams body weight, of this, 2.7 mg./grams was urine, 2.3 mg./grams was feces and 8.9 mg./grams was "net loss" through evaporation from the lungs, etc.

The increases (34.5-39.5%) in "net loss" were significant at 8000 ft. and above, in urine (107.4-631.8%), at all altitudes, in feces (75.5-153.4%), at 8000 ft. and above. As a rule they were proportional to the altitude.

A second group of younger adult rats exposed similarly to 24,000 and 28,000 ft. showed increases in "net loss" and feces that were consistent with those of the first group, but the increases in urine were considerably less than were expected.

It is concluded that in adult rats the thresholds to anoxia for increased "net loss" and feces are near 8000, while that for urine is near 4000 ft., and that anoxia increases body weight loss in proportion to its severity over the range studied.

Effects of carbon dioxide administration on cerebral metabolism in hypoxia. W. E. STONE, J. E. WEBSTER (by invitation), J. KOPALA (by invitation) and E. S. GURDJIAN (by invitation). *Wayne Univ. College of Medicine and Grace Hospital, Detroit.* Lactic acid, acid soluble phosphorus compounds, glucose and glycogen were determined in cerebral tissue frozen *in situ* (morphinized

dogs) Hypoxia of 15 minutes' duration produced by administration of oxygen-nitrogen mixtures caused increased cerebral lactic acid, partial decomposition of phosphocreatine, no significant changes in adenosine triphosphate, glucose or glycogen. Addition of 5-6% carbon dioxide to the gas mixture diminished the effects of hypoxia. The beneficial effect of carbon dioxide was due in large part to increased oxygen tension of the arterial blood (respiratory response). Improved cerebral circulation also appeared to be a factor since the effect of carbon dioxide on cerebral lactate was more evident when lactate was plotted against arterial oxygen tension than when lactate was plotted against cerebral venous oxygen tension. Even in the latter case a small effect of carbon dioxide was apparent.

Cerebral levels of lactate and phosphocreatine correlated better with the oxygen tension of cerebral venous blood than with that of arterial blood. The cerebral changes showed no correlation with changes in arterial or cerebral venous carbon dioxide tension or pH, at comparable levels of cerebral venous oxygen tension.

Hyperventilation due to the hypoxia caused a drop in blood carbon dioxide tension which was diminished but not always completely counteracted by administration of 5-6% carbon dioxide. At normal oxygen levels, addition of 5-6% carbon dioxide to the respired gas mixture increased blood carbon dioxide tension but did not affect the levels of the cerebral constituents studied.

An instantaneously recording cardi tachometer R. E. STURM (by invitation) and E. H. WOOD, *Acceleration Lab., Mayo Aero Medical Unit, Rochester, Minnesota*. An instrument has been developed which continuously and instantaneously records the heart rate. In principle, the device consists of an electrical circuit which deflects a galvanometer at a constant rate, the swing of the galvanometer is interrupted and returned to the zero position instantaneously ($\frac{1}{100}$ second) by the R-wave of the electrocardiogram. Thus, the length of the galvanometer deflection is proportional to the interval between successive R-waves and when used with a suitable camera the device plots a graphic record of the heart rate with each heart beat.

The instrument was designed to allow convenient study of the rapid changes in heart rate which occur in man during exposure to positive acceleration and for this purpose has been extensively and satisfactorily used in this laboratory for some years. It has been found that throughout the period of progressive failure which is encountered during the first six to eleven seconds of exposure to positive g the heart rate rapidly increases. If the acceleration is maintained, the period of compensa-

tion then occurs and this increase is checked and the heart rate is usually slowed.

Although as used in these studies the instrument is activated by the R-wave impulses of the electrocardiogram, it can easily be adapted to record the pulse rate from opacity, volume or pressure pulse impulses. Also, by appropriate modification it can be used to record the instantaneous rate of occurrence of other phenomena which produce or can be made to produce changes in electrical potentials. [Work done under contracts with (1) *United States Army Air Forces, Wright Field, Dayton, Ohio*, and (2) *the Office of Scientific Research and Development, National Research Council, Washington, D. C.*]

The effect of massage upon denervation atrophy of skeletal muscle MITZI I. SUSKIND (by invitation), Norma M. Hajek (by invitation) and H. M. HINES, *Dept. of Physiology, State Univ. of Iowa, Iowa City* (Read by title). The gastrocnemii of cats were subjected to total denervation either by sectioning or crushing the tibial nerves. The gastrocnemius of one limb was massaged twice per day for periods of 5 minutes. The denervated untreated muscle of the contralateral limb was used as a control. Studies were made at various times after denervation of the weight and strength as measured by maximal isometric tension responses of the treated and untreated muscles.

The denervated muscles which received massage treatments were consistently heavier and stronger than their controls. When the treatments were extended into the periods of reinnervation and regeneration the differences tended to be equalized. The beneficial effects of massage were more apparent upon strength than upon weight changes. Electrical stimulation of the denervated gastrocnemius of the cat was found to be more effective in the retardation of weight loss than of strength loss.

Explosive decompression—human subjects (motion picture) H. M. SWEENEY and H. M. JOFFE (by invitation) *Aero Medical Lab., Air Technical Service Command, Wright Field, Dayton, Ohio*. The effect on the body of rapid loss of pressure in pressurized aircraft (explosive decompression) results from the rate and extent of expansion of internal body gases. The rate is dependent upon the volume of the pressurized container, size of aperture, and differential pressure. The extent of expansion is dependent upon the differential pressure and the pressure altitude at which decompression takes place. With these basic factors in mind, progressive experimental decompressions were done on human subjects to prove the safety of useful pressure differentials for the various types of aircraft.

More than two hundred human experiments have been done to prove the safety of the presently recommended pressure differentials. At the mo-

ment of decompression, the subjects experienced a sense of inflation in the chest and abdomen and a rush of air from the mouth and nose. Few cases of gas pain were encountered, and roentgenograms to depict the amount of gas harbored in the gastrointestinal tract did not show any positive correlation. Ear pain was not experienced.

(This is a 16 mm sound safety film and takes approximately 23 minutes to run at a speed of 24 frames per second.)

The nature of circulating estrogen. CLARA M SZEGO and SIDNEY ROBERTS (introduced by Hudson Hoagland) *Worcester Foundation for Experimental Biology, Shrewsbury, Mass.* The presence in the circulation of injected estrogen is inadequate to cause uterine water imbibition. Thus, this response does not occur in the ovariectomized, eviscerated rat (Szego & Roberts, *Endocrinology*, 36: 104, 1945).

In an attempt to elucidate the conditions underlying estrogen activity *in vivo*, we undertook studies of the nature of circulating estrogen. The investigations involved (a) chemical fractionation procedures, (b) behavior of blood estrogen with respect to artificial membranes.

(a) The chemical fractionation procedures included, in part, blood protein precipitation with cold acetone, followed by extraction of the supernatant material and of the undenatured protein subjected to partial hydrolysis.

The results on bloods of several species, including gravid and gonadotrophin injected animals, indicate that

1. there is very little free estrogen in blood,
2. a large and constant fraction (67%) appears to be intimately bound to protein,
3. the estrogen in the supernatant material is in relatively simple conjugated form, possibly partly the glycuromide, and partly the simple sodium salt.

(b) We have found pure estrogens in simple sodium salt form or in the free state dialyze quantitatively through a collodion membrane. Moreover, natural blood estrogen is also freely dialyzable in amounts which compare quantitatively with values found by exhaustive chemical extraction.

The data indicate that the postulated estrogen-protein complex probably dissociates in accordance with the mass action law. This suggests that estrogen bound to protein is potentially available for physiological action.

The above results bear on the fundamental problem of steroid transport and activity *in vivo*.

Visual areas I and II of cerebral cortex of rabbit. S. A. TAYLOR, C. N. WOOLSEY, J. M. THOMSON, (by invitation), *Wilmer Ophthalmological Inst and Dept of Physiology, Johns Hopkins Medical School.* The cortex of (chinchilla) rabbit which

responds electrically to photic stimulation of the eye, includes Rose's areas Striata, Parastrata, and Occipitalis. This is divided into a posteromedial three-quarters (Area I), and an anterolateral quarter (Area II), by a diagonal line representing the retinal decussation or vertical meridian through gaze. This meridian in the visual field lies about 20° from the sagittal plane of the anesthetized animal. Areas I and II are projected with reversed topography, as with cat's 17 and 18. Area II coincides visually with area I along the vertical meridian. The lateral field has been found represented out to 100° in area II and to 150° in area I.

Central vision has a region of high cortical resolution (about $\frac{1}{4}$ that of cat), which suggests that the rabbit can utilize parallel fixation. The binocular fields I and II occupy about 2½ mm of cortex on either side of the vertical meridian line. This covers nearly 45° of contralateral field seen through the ipsilateral eye. Projection of ipsilateral field has not appeared.

The horizontal meridian projects close to the posterolateral border of the visual cortex, in both I and II, except for a strong medial dip about the vertical meridian line, through central vision. Consequently the upper visual field has small representation except here. The projection of lower field below 15° is compressed similarly. There appears at about 70° horizontally from centralis, a second region of slightly increased cortical resolution (like the second fovea of birds). This would serve lateral attention without movement. [This work was aided by a grant from the John and Mary R. Markle Foundation.]

The axial stream in the aorta of dogs and cats. A. N. TAYLOR and H. J. RALSTON (introduced by Eric Ogden) *Dept of Physiology, Univ of Texas Medical School, Galveston, and College of Physicians and Surgeons, San Francisco.* The insertion of a thin walled glass tube into the arteries of dogs and cats to observe the flow pattern of injections of India ink has been described by us (Ralston and Taylor, *Am Jour Physiol* vol 144, p 706, 1945). The normal flow from the left ventricle to the femoral artery appears streamlined (laminar, viscous) and the axial filament does not appear to be diverted by the major branches (coeliac, mesenteric, renal). Timing the passage of ink from the right and left ventricles to the femoral artery gave measurements of the pulmonary circulation time and of the velocity of the blood in the arterial circulation. The arterial velocity, thus studied, was the same for the cats and dogs (ca 17 cm/sec) and Reynolds' number in these experiments has a value well below that for turbulent flow. Pulmonary circulation time was 2 to 5 seconds in both cats and dogs. The experimental procedure may have affected the circulation. Any solution introduced into

the circulatory system probably assumes the pattern of a broad band with a parabolic front. At increasing distances from the point of injection the front is progressively more pointed and ultimately becomes an axial filament. The velocity of the front of this axial filament represents the maximum velocity attained and is twice the average velocity of the blood stream. This should be borne in mind in the interpretation of circulation times.

Some effects of extreme heat and humidity on man CRAIG L. TAYLOR and JOHN P. MARRANGER (by invitation) *Acro Medical Lab., Air Technical Service Command, Wright Field, Dayton, Ohio*. Further studies of the heat tolerance of sitting resting man have been carried out. In the present series five nude subjects were tested in ten environments which varied in environmental temperature from 100 to 154°F and vapor pressure from 10 to 46 mm Hg. Rectal and skin temperatures were continuously determined by thermocouples, heart rates by palpation, and sweat loss by means of a balance Drip sweat was collected and measured.

Since elevations of heart rate, skin temperature, and sweat loss were found in all exposures (and of rectal temperature in all but the mildest conditions) a varying degree of hyperthermia was the rule. Evaluation of the four physiological measures showed that heart rate, and skin and rectal temperatures could be combined to yield an index of the degree of heat strain, but that sweat loss could not be included in such an index because it varied with certain environmental conditions independently of the degree of hyperthermia. Thus, for equivalent elevations of heart rate, and body temperature, sweat loss was higher if (a) the vapor pressure was low, (b) the air movement was increased, and (c) clothing was worn.

At constant vapor pressure (10 mm Hg), the index of heat strain increases disproportionately with environmental temperature. At constant temperature (100°F), the index does not vary significantly with humidity until approximately 30 mm Hg vapor pressure (60% RH) when it increases markedly. These data show that quite different physiological effects result from exposure to hot-dry as compared with hot-humid environments.

The effect of six months of semi-starvation on the maximal oxygen intake HENRY LONGSTREET TAYLOR *Lab., of Physiological Hygiene, Univ. of Minnesota, Minneapolis, Minnesota*. The maximal oxygen intake was determined at 3 month intervals on seven men who underwent six months of semi-starvation (cf. Keys, *Fed. Proc.* 1946). Expired air was collected from 1'45" to 2'45" of a three-minute run at seven miles per hour and at grades which varied from zero to 12.5 per cent, depending on the capacity of the subject. In each experimental period, determinations were made at

two work levels to demonstrate that maximal O₂ intake had been attained. Average values of 3.35, 2.33 and 1.96 liters of oxygen consumption per minute were obtained for the control period and 12 weeks and 24 weeks of semi-starvation respectively. Expressed as cc of oxygen consumption per kilo, the values were 18.2, 41.7 and 37.1. The subjects had definite edema at 12 and 24 weeks of starvation. Active tissues, calculated from measurements of body specific gravity (fat), thiocyanate space, blood volume and an estimated figure for bone were 30.5 kg in the control period and 18.0 at 24 weeks of semi-starvation. Oxygen was used at a rate of 0.110 liters per kg of active tissue during the control period and 0.109 liters per kg at the end of semi-starvation. Since the blood hemoglobin concentration declined 22 per cent, it appears that in starvation either the arterial-venous difference increased or there was an increase in cardiac output per unit of active tissue. [This work was supported in part under a contract with the Office of Scientific Research and Development. Support from other sources will be acknowledged in final publication.]

Effect of p-aminopropiophenone induced methemoglobinemia on the oxygenation of working muscle in human subjects JAY TEPPERMAN¹ and OSCAR BODANSKY² (by invitation) *Biochemistry Section, Medical Division, Chemical Warfare Service, Edgewood Arsenal, Md.* It has been found that methemoglobinemia induced by p-aminopropiophenone (Vandenbelt et al., *J. Pharm. Exp. Therap.* 80:31, 1944) protects dogs against the lethal actions of hydrocyanic acid and of cyanogen chloride, and that the efficacy of this protection is related to the degree of methemoglobinemia at the time of gassing (Bodansky and Jandorf, to be published). Since p-aminopropiophenone was considered to be a potential prophylactic agent against cyanide poisoning in man, it was necessary to estimate the effect of methemoglobinemia on the oxygenation of working muscle in human subjects.

The rise in blood lactic acid over the resting level following a three-minute bout of measured exercise on the cycle ergometer was used as a test of work efficiency. Six healthy young male subjects, after training on the cycle ergometer for three weeks, showed good consistency of performance in tests performed on consecutive days at the same work load. When they worked at the rate of 4680 foot-pounds per minute, lactate rises were small (from 10 to 25 mg per cent), and exercise in the presence of 7.7 to 17.9 per cent methemoglobinemia resulted in no excessive accumulation of lactate in the blood. When the same men exercised at rates varying between 6550 and 8420 foot-pounds per minute in the presence of 10.0 to 19.8 per cent methemo-

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globinemia, their maximal blood lactate rises were 15 to 56 per cent higher than were their peak concentrations on the control day

The effect of thiouracil administration on the succinoxidase and cytochrome oxidase of rat liver SAMUEL R. TIFTON and W. L. NIXON (by invitation) *Dept. of Physiology and Pharmacology, Medical College of Alabama, Birmingham, Alabama* Oral administration of 100 mgs of thiouracil per day to hooded rats of the Long-Evans strain (weight 150-250 grams) for 3-4 weeks led to a significant decrease in the activity of the succinoxidase and cytochrome oxidase of the liver. Controls showed a liver succinoxidase QO_2 of 108.7 ± 3.53 (S.E.) and a cytochrome oxidase QO_2 of 410.6 ± 18.94 . After thiouracil the values were 77.4 ± 12.96 and 315.3 ± 58.99 respectively. Subcutaneous injection of 2 ml of thyrotrophic hormone daily for 1-2 weeks resulted in increased QO_2 values for liver succinoxidase (133.0 ± 4.1) and cytochrome oxidase (731.4 ± 18.24). If thiouracil and thyrotrophic hormone were given simultaneously the enzyme values did not differ appreciably from those of control rats. Thiouracil administration to thyroidectomized rats had no significant effect on the liver enzymes. A 50 mg % solution of thiouracil had no effect on the liver respiratory enzymes *in vitro*. It appears that the thiouracil effect on the succinoxidase and cytochrome oxidase of the liver is due to indirect action of the drug on the thyroid gland and its production of thyroid hormone and not to a direct action of the drug on the liver cell. [Aided by a grant from the Univ. Research Committee.]

Some properties of maximal electroshock seizures: JAMES E. P. TOMAN, EWART A. SWINYARD² (by invitation), and LOUIS S. GOODMAN. *Depts. of Physiology and Pharmacology, Univ. of Utah School of Medicine, Salt Lake City, Utah* Seizures produced in rabbits, cats, and rats by alternating current intensities more than 20% above threshold were constant in pattern and duration, and independent of intensity and duration of stimulation. Such "maximal" seizures were almost entirely tonic in character, and were predominantly flexor during the first one third and extensor thereafter. Continuous or intermittent stimulation during maximal seizures did not modify them, nor did previous lowering of threshold by metrazol or by cellular hydration due to acute extracellular electrolyte depletion (isomolar glucose, 1 p).

The extensor tonic component of maximal seizures could be abolished by frequent repetition or by clinically effective antiepileptic drugs in doses not causing neurological deficit. Diphenylhydantoin and phenobarbital were effective in doses

less than one-half that required to produce neurological signs, tridione was effective in 70% of the neurological dose, sodium bromide was just effective at depressant dose levels. Other barbiturates, hydantoinates, and oxazolindione derivatives, and benzimidazole were found effective.

Ability of drugs to abolish the tonic extensor component of maximal seizures was independent of their relative ability to increase normal electroshock seizure threshold. For example, diphenylhydantoin was effective in doses which failed to increase seizure threshold, and remained effective even in toxic doses which lowered threshold.

EEG observations during maximal seizures and following their modification by drugs suggested that antiepileptic agents may act by some mechanism other than increase in neuronal threshold to reduce the rate and quantity of energy expenditure in seizure discharges.

A comparison of time relations in convulsive and nonconvulsive responses to cortical stimulation¹ (Read by title) JAMES E. P. TOMAN and E. A. SWINYARD² (by invitation) *Dept. of Physiology and Pharmacology, Univ. of Utah School of Medicine, Salt Lake City, Utah* Voltage-capacity data for non-convulsive cortical discharges elicited by single cortical shocks in unanesthetized rabbits reveal an excitation constant of the order of one millisecond. Likewise, for production of seizures by alternating current of variable frequency, or by repetitive thyatron discharges of variable frequency or pulse duration, the calculated excitation constants compare with those for peripheral neurones. However, if total duration of stimulation is varied while pulse form and frequency remain constant, the time for 50% development of excitatory state is approximately 2 seconds. A similar period for 50% decay of excitatory state is found when seizures are elicited by summation of brief inadequate stimuli.

For non-convulsive EEG responses in rabbits, the recovery process is half completed in 0.1 to 0.2 seconds when thresholds are tested by a second shock. For seizures, 3 to 4 minutes are required for 50% recovery in rats and rabbits.

As reported elsewhere in these Proceedings, seizures elicited in rabbits, cats, and rats by stimuli above a critical threshold adhere to the "all-or none" law in respect to their independence of stimulus intensity. The brain is completely inexcitable to intercurrent stimulation during such "maximal" seizures. Their unmodifiability suggests that the brain may act as a maximally self-reexciting synectism when central inhibition is temporarily abolished during seizures. Such a unitary excitable system might be expected to

¹ Aided by a grant from the Research Fund, University of Utah School of Medicine.

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have properties qualitatively similar to those of individual neurones, but with time characteristics of a different order of magnitude

Effect of serum and its fractions on acetylcholine synthesis CLARA TORDA and HAROLD G WOLFF *New York Hospital and the Depts of Medicine (Neurology) and Psychiatry, Cornell Univ Medical College, New York N Y* In the presence of serum or spinal fluid of patients with myasthenia gravis less acetylcholine is synthesized by an *in vitro* frog brain preparation than in the presence of serum or spinal fluid from healthy subjects (C Torda and H G Wolff, *Science*, 98 221, 1913, 100 200, 1944, *J Clin Invest*, 23 619, 1944)

The question consequently arises as to the nature of the substances in normal serum that affect acetylcholine synthesis This subject is being investigated by fractionating serum ultrafiltrates in various ways and comparing the action of the fractions with the results obtained by adding to the enzyme preparation compounds that are presumably present in the fractions used To date there is good agreement between the two types of studies

Referred somatic pain does not follow a simple "segmental" pattern JANET TRAVELL and NOLTON H BIGELOW (introduced by McKee Cattell) *Dept of Pharmacology, Cornell Univ Medical College, New York, N Y* During treatment of skeletal muscle pain by local infiltration in a large group of patients, we mapped the distribution of pain referred from various muscles In such subjects, needling spontaneous "trigger areas" induces referred pain as clearly perceived as that induced by hypertonic saline in normal muscles The distribution of pain referred from a given site is essentially the same by either technic

Several significant pain patterns are illustrated, some reduplicated in as many as 100 subjects Like others, we found that the distribution of referred somatic pain is remarkably constant for the structure stimulated, which implies fixed anatomical pathways We noted, however, that pain reference may exhibit a pattern which cannot be explained by the prevailing concept that referred somatic pain follows a simple "segmental" or nerve root distribution Detailed analysis of pain patterns showed that although pain referred from different sites may fall entirely within the reference area attributed to one segment (Kellgren *Clin Sc*, 4 35, 1939, Inman and Saunders, *J Nerv and Ment Dis*, 99 660, 1944), it is usually perceived respectively in different portions of this area Furthermore, the reference from a single site may comprise fragments of several "segmental pain areas" without including any one entirely, or may take in a whole "segmental area", skip the adjacent one and reappear distally Consequently, referred somatic pain must involve special spinal pathways

The bearing of these findings on the mechanism

of pain reference from somatic structures is discussed

Influence of thyrotropin on iodine metabolism in the thyroid glands of hypophysectomized rats W P VANDER LAAN and A BISSEIL (introduced by E B Astwood) *Dept of Medicine Tufts Medical School and the Jos H Pratt Diagnostic Hospital, Boston* Observations were made concerning the influence of thyrotropin on the iodine concentration in the thyroid glands of 21 to 25 day-old rats which had been hypophysectomized and fed 0.1% propylthiouracil 48 hours before the injections of thyrotropin were begun It was found that the iodine concentration fell and that this fall was a function of time and dose When 5 mg of thyrotropin (3 to 4 Junkmann-Schoeller units per mg) were daily injected subcutaneously the thyroid iodine concentration fell in 5 days from the initial value of 60 to 9.4 mg per 100 grams Between the amounts of 0.03 and 1.0 mg thyrotropin given daily for 5 days the decrease in thyroid iodine concentration was proportional to the dose This method proved useful for assay purposes It was found that in hypophysectomized rats neither propylthiouracil nor thyrotropin alone lowered the thyroid iodine concentration in the 5 day period

By preventing thyroid hormone synthesis with propylthiouracil and by depleting the thyroid iodine with thyrotropin it was possible to study the ability of the thyroid gland of hypophysectomized rats to fix iodine after thyrotropin had been withdrawn and to incorporate iodine into protein after both thyrotropin and propylthiouracil had been withdrawn

Action of certain autonomic agents on the blood pressure rise produced in dogs by acute oxygen lack EDWARD J VAN LIERE and DAVID F MARSH (by invitation) *Depts of Physiology and Pharmacology, School of Medicine, West Virginia Univ, Morgantown* Anoxic anoxia was produced in barbitalized and in urethanized dogs by administering six, seven, and nine per cent oxygen atmospheres and asphyxia by obstructing the trachea The ensuing rise in blood pressure from either of these procedures is presumably due to afferent impulses from the carotid and aortic bodies to the vasomotor center leading to efferent sympathetic release

Ergotamine blocks this rise in blood pressure by inhibiting the carotid and aortic bodies, and oxygen lack then produces a fall in blood pressure similar to that seen in animals that have had these receptors denervated This effect occurs even with doses of ergotamine that are insufficient to reverse the effects of epinephrine or to block the rise in blood pressure produced by ephedrine

Yohimbine produced similar effects, but it is only effective in doses that are truly sympatholytic Adrenolytic doses of piperidinomethylbenzodioxan

(933F) were ineffective in antagonizing the rise in blood pressure

Like other sympathetic induced rises in blood pressure, the effects are potentiated additively by epinephrine and ephedrine, and synergistically by cocaine

Protection against acceleratory forces by CO₂ inhalation L VAN MIDDLESWORTH (by invitation) and S W BRITTON *Physiological Lab, Univ of Virginia Medical School* Increased tolerance to positive acceleratory forces has been demonstrated with monkeys, cats and dogs which inhaled CO₂/O₂ mixtures before and during the acceleration Brachial arterial pressure, EKG, and EEG were continuously recorded in more than 200 exposures of 30 animals 13-20 percent CO₂ in O₂ administered (at sea level) to monkeys for 18-180 seconds or to dogs 50-180 seconds prevented about 40 per cent of the blood pressure changes ordinarily observed at 4 "plus G" per 10 second exposure When this mixture was inhaled for more than 300-400 seconds the beneficial effect was lost

The turbulent flow factor in cardiac work MAURICE B VISSCHER and ALLAN HEMINGWAY *Univ of Minnesota* Attention has been called recently¹ to the fact that the use of the Bernoulli theorem, involving the assumption of a frictionless fluid, in calculating the work of the heart in giving ejected blood kinetic energy, is improper The authors cited properly insist that when streamline flow occurs the central shells of the moving stream have a greater velocity than do the outer shells and that the kinetic energy of viscous fluids can be estimated only by such a calculation as they develop

However the above authors fail to state that their calculations are valid only for instantaneous velocities Actually during the course of a single ejection phase a time velocity function must be considered, as was pointed out by Katz²

Unfortunately, Ralston and Taylor¹ stated that in calculating cardiac work "the classical (frictionless flow) formula should be used when the flow is known to be turbulent" This assertion ignores the fact that when flow is turbulent the energy cost of giving forward velocity is greater than the kinetic energy of forward movement, because in turbulence a large share of the energy expenditure is dissipated in rotational movement It is precisely because extra energy must be supplied to overcome the increased resistance due to turbulence that conditions which cause turbulence raise the work of the heart Thus, although it is roughly true that the kinetic energy of forward motion in turbulent flow is approximately $\frac{1}{2}$ in v^2 , it is an error to suggest that the work of the heart may be measured by that expression when flow is turbulent

Additional observations on the prophylaxis of experimental renal hypertension with renal extracts G E WAKERLIN, H MINATOYA (by invitation) and T LEFCO (by invitation) *Dept of Physiology, Univ of Illinois College of Medicine, Chicago* (Read by title) We have previously reported that daily intramuscular injections of certain renal extracts for three months before and after bilateral constriction of the renal arteries, protected 5 of 13 dogs against the development of experimental renal hypertension After three and one-half to four years of normotension, four of the five protected dogs showed a gradual increase in blood pressure over a period of six to ten months to definitely hypertensive levels The fifth protected dog is still normotensive The mechanism of this long period of prophylaxis is unexplained (Fed Proc, 4 24, 1945)

We have other evidence indicating that the prophylactic effect of partially purified hog renal extract containing renin may last for many months Thus two of three dogs treated daily and intramuscularly for four months with partially purified hog renal extract in a dose of 1 and 2 grams respectively of fresh renal cortex equivalent per kg but not subjected to bilateral renal artery constriction until one and one-half and two and one half years later, were protected against experimental renal hypertension None of the three dogs showed anti-renin in their serums at the time of the renal artery constrictions Likewise one of two dogs previously given semi-weekly intravenous injections of the same hog renal extract in a dose of 0.1 gram of fresh renal cortex equivalent (containing 0.1 Goldblatt unit of renin activity) per kg for sixteen months, was protected against experimental renal hypertension Neither of these animals showed anti-renin either during the injection period or at the time of constriction

Further experiments are planned to produce maximum prophylaxis, to elucidate its mechanism, and to fractionate for the active principle [This work was aided by grants from the John and Mary Markle Foundation and the Graduate School Research Fund of the Univ of Illinois]

The effect of unilateral nephrectomy on the development and maintenance of experimental renal hypertension G E WAKERLIN, T LEFCO (by invitation), and H MINATOYA (by invitation) *Dept of Physiology, Univ of Illinois College of Medicine, Chicago* (Read by title) Thirty-eight dogs were subjected to unilateral renal artery constriction and subsequent contralateral nephrectomy for the production of experimental renal hypertension Of 17 of these animals subjected to nephrectomy 0-20 days following renal artery constriction, malignant hypertension developed in 6, negligible to poor hypertension in 8, and satisfactory hypertension in 3 Of the 21 dogs subjected to

¹Am J Physiol 144 705 1945

²Ibid 97 579 1932

nephrectomy 20-100 days following renal artery constriction, 1 developed malignant hypertension, 5 showed poor hypertension, and 15 showed satisfactory hypertension. These results suggest that following unilateral renal artery constriction, the unoperated contralateral kidney stimulates the hypertensive effectiveness of the renal artery constricted kidney, the stimulation reaching more or less of a plateau within the first 20 days. Whether this influence is related to the known anti-hypertensive effect of the unoperated kidney or to the disappearance of renin from it (Fed Proc, 6 1946) remains to be determined.

Twenty-two dogs with bilaterally constricted renal arteries were subjected to unilateral nephrectomy after four to forty months of satisfactory hypertension. The kidney removed was normal-sized in 14 animals and definitely smaller to atrophic in 8. There was a significant decrease in blood pressure in 3 of the first group and in 1 of the second. The remaining 18 animals showed no significant change in their hypertension. The results suggest that once established, the hypertension produced by bilateral renal artery constriction is not affected by unilateral nephrectomy in a majority of dogs and that in a minority, removal of a normal-sized kidney is as likely to produce a decrease in pressure as removal of an atrophic kidney. [Aided by grants from the John and Mary R Markle Foundation and the Graduate School Research Fund of the Univ of Illinois]

The effect of unilateral renal artery constriction on the renin content of the contralateral kidney. G E WAKERLIN (with the technical assistance of T Lefco and H Minatoya) *Dept of Physiology, Univ of Illinois College of Medicine, Chicago*. Study was made of the renin content of the contralateral kidney of dogs at intervals of 0 to 100 days following unilateral renal artery constriction. At 0 days, the contralateral kidney of 4 dogs showed normal (100%) renin content (approximately 1 Goldblatt unit per gram of fresh renal cortex), 5 days after unilateral renal artery constriction, the contralateral kidney of one dog showed 0% renin and that of a second animal, 100% renin, after 10 days (2 dogs) 10% and 100% renin, and after 15 days (3 dogs) 0%, 0%, and 100% renin. Twenty dogs nephrectomized contralaterally 20-100 days following unilateral renal artery constriction showed 0% renin in the contralateral kidney with 3 exceptions (15%, 15%, and 30%). By contrast the renin content of the individual kidneys of 12 normal dogs assayed 90-100%. Likewise the renin content of the contralateral kidney of 11 dogs 10 to 14 months after renal artery constriction of the contralateral kidney was 100% in 8, 20% in 2, and 0% in 1 animal. That the renin content of the unoperated contralateral kidney returns relatively quickly following renal artery constriction is sug-

gested by preliminary experiments in which the renin content of three contralateral kidneys unoperated for 90, 100, and 120 days was found to be 45%, 0% and 55% respectively, 24, 48, and 48 hours after arterial constriction.

The significance of the disappearance of renin from the contralateral kidney in relation to its known antihypertensive effect and to the pathophysiology of experimental renal hypertension remains to be determined. Studies of the concentration of other enzymes in the non-renin kidney, as well as an assay of its antihypertensive potency, are planned. [Aided by grants from the John and Mary R Markle Foundation and the Graduate School Research Fund of the Univ of Illinois]

Treatment of experimental renal hypertension with beef and sheep renal extracts. G E WAKERLIN, WAYNE DONALDSON (by invitation), and OLIVER KAMM (by invitation) *Dept of Physiology, Univ of Illinois College of Medicine, Chicago, and Research Labs, Parke, Davis & Company, Detroit*. (Read by title.) In a further study of the mechanism of the antihypertensive activity of hog renal extracts previously reported (Am Ht J, 25 1, 1943, J Pharm & Exper Ther, 81 101, 1944, and Fed Proc, 4 74, 1944), we treated two hypertensive dogs each for six months daily and intramuscularly with partially purified beef renal extract containing renin, partially purified sheep renal extract containing renin, and hog muscle extract prepared after the manner of the renal extracts, in a 2 gram equivalent dose of fresh renal cortex or muscle per kg. The renin activity of the beef extract was approximately 1 Goldblatt unit per gram of fresh tissue equivalent and that of the sheep extract approximately 0.5 Goldblatt unit. None of the six dogs showed any significant change in blood pressure. The four renal extract injected dogs showed low to moderate serum antirenin titres during treatment whereas the two muscle extract injected dogs showed no antirenin. The results suggest that the antihypertensive potency of hog kidney is greater than that of beef and sheep kidney. [This work was aided by grants from the John and Mary R Markle Foundation and the Graduate School Research Fund of the Univ of Illinois]

Treatment of experimental renal hypertension with hog renal extract fractions. G E WAKERLIN, WAYNE DONALDSON (by invitation), and OLIVER KAMM (by invitation) *Dept of Physiology, Univ of Illinois College of Medicine, Chicago, and Research Labs, Parke, Davis & Company, Detroit*. (Read by title.) One year ago (Fed Proc, 4 73, 1945) we reported that in our endeavor to fractionate and purify the antihypertensive potency of partially purified hog renal extract containing renin, we found only one of the nine fractions studied (a dialysis residue) to be effective

antihypertensively During the past year we have studied the antihypertensive activity of three fractions of this dialysis residue The dissolved spontaneous precipitate of the dialysis residue was injected daily and intramuscularly in two hypertensive dogs for four and one-half months in a dose of 10 grams of fresh renal cortex equivalent per kg with moderate and slight antihypertensive effects respectively The dissolved 50 per cent hydroacetone precipitate of the dialysis residue was similarly assayed in two hypertensive dogs for eight months with excellent and slight antihypertensive effects respectively One of the proteins of the last fraction was separated and assayed in a dose of 20 grams of fresh renal cortex equivalent per kg for six and one half months in two hypertensive dogs with slight and negative antihypertensive effects respectively These three fractions retained 50, 2-5, and 0 per cent of the renin activity of the original partially purified hog renal extract The antirenin titres of the dog serums during treatment were comparatively low but there appeared to be a relationship between the titres and the antihypertensive responses, contrary to observations previously reported We are continuing our efforts to fractionate for the antihypertensive potency of hog kidney and to determine the mechanism of the antihypertensive effect [*This work was aided by grants from the John and Mary R Markle Foundation and the Graduate School Research Fund of the Univ of Illinois*]

The effects of ethyl alcohol on the isolated heart K G WAKIM *Indiana Univ Medical School, Bloomington and Indianapolis* (Read by title) For a study of the effects of various concentrations of alcohol on cardiac activity, the turtle heart was carefully dissected out with the sinus venosus, atria, and ventricle intact A small slit was made in the left auricle into which a special glass cannula was introduced and anchored by ligature The frenalum attached to the apex of the ventricle was connected by means of a thread to the recording lever for kymographic registration of heart beats Oxygenated Ringer-Locke solution was used for perfusate After taking control tracings of cardiac activity, various amounts of absolute ethyl alcohol were mixed with the perfusate and their effects on the isolated heart were recorded

The effects of amounts lower than 4 cc of absolute alcohol per liter were meager, but the addition of 4 to 10 cc of absolute alcohol per liter of perfusate led to a slight reduction in the amplitude of cardiac contractions Ten to 50 cc per liter caused a gradual intensification of the effects of alcohol on the heart, namely, a progressive dilatation with reduction in amplitude, force and rate of the beat until at a concentration of about 10 to 50 cc of alcohol per liter the heart stopped in an engorged state The ventricle often fibrillated when the higher concen-

trations of alcohol were used However, these effects of alcohol were reversible and the heart could be repeatedly recovered by perfusing it with Ringer-Locke solution even after it had been under the influence of the perfusate containing the higher concentrations of alcohol for about twelve minutes

The influence of ergotoxine on survival time of rats in shock K G WAKIM *Indiana Univ Medical School, Bloomington and Indianapolis* (Read by title) Secondary shock was produced by application of a clamp to each hind leg of the rat as described by Haist & Hamilton (*J Physiol* 102 471, 1944) The clamps were left on overnight for 15½ hours Of the 50 rats whose survival time was accurately determined, 25 were given each 5 mg of ergotoxine intraperitoneally 10 minutes before the clamps were removed and their survival time was compared with that of the other 25 rats which were not given ergotoxine Soon after removal of the clamps, the limbs became purplish and swollen The average survival time of those receiving ergotoxine was 1.9 hours while those without ergotoxine had an average survival time of 6.4 hours There was no significant difference in red cell counts or hemoglobin concentration between those given ergotoxine and those without ergotoxine

Dale and others demonstrated that ergotoxine paralyzes the vasoconstrictor sympathetics and, consequently, abolishes the pressor effects of adrenalin This effect of ergotoxine was confirmed on anesthetized rats whose blood pressure was registered by means of a mercury manometer connected to a cannula introduced into the abdominal aorta at its bifurcation to the common iliac Sodium citrate was used to prevent coagulation of the blood in the cannula A few minutes after intravenous administration of 2 mg of ergotoxine, the usual strong pressor effect of adrenalin that was observed prior to ergotoxine administration could not be elicited after ergotoxine Either a slight fall or no effect on the blood pressure was obtained by the same dose of adrenalin intravenously administered after ergotoxine

These findings justify the conclusion that the paralysis of the sympathetic vasoconstrictors produced by ergotoxine abolished the compensatory vasopressor reflex during the development of secondary shock, interfered with circulatory adjustments, and consequently shortened the survival time of the animals

The response of the Triceps Surae of the adrenalectomized and normal rat to single and multiple stimulation SHEPPARD M WALKER (by invitation) and A S GILSON, JR *Dept of Physiology, Washington Univ School of Medicine, St Louis* Isometric responses of the triceps surae of 100 grams rats were recorded by an optical myograph The stimulator generally used yielded a diphasic shock, the duration of the main com-

ponent being 0.2 msec. Stimulating electrodes were placed at the two ends of the muscle or on the cut sciatic nerve. Tension is expressed as gram per gram fresh muscle.

Responses from curarized animals show mean tensions of 390 for normal and 430 after adrenalectomy. A stimulus strength 6x maximal applied through the muscles of normal and of adrenalectomized animals gave mean tensions of 386 and 576, respectively. Single stimuli applied to the sciatic nerve produced tensions 40 per cent greater than those from curarized animals when 100x maximal for normal rats but only 2x maximal for adrenalectomized rats. Muscle action potentials from supramaximal contractions indicate repetitive responses from part of the muscle units.

Peak tensions in tetanus were slightly diminished after adrenalectomy. During 2 sec stimulation of curarized muscles (225 per sec) tension curves from adrenalectomized rats fell slightly more than those from normals. When the sciatic nerve was stimulated at this rate, diminution of tension was more rapid in normals.

Four hundred stimuli at 2 per sec caused tension reduction of less than 5 per cent in normals but of 52 per cent in adrenalectomized animals.

Thus, although the muscles of adrenalectomized animals show abnormal fatigability, there is increased excitability of nerve trunks and at least normal neuro-muscular conduction at high frequency.

Magnetic stimulation of the human retina. G. WALSH (by invitation), H. BARLOW (by invitation), and H. I. KOHN. *Dept of Biology, Mass Inst of Technology, Cambridge, and Harvard Medical School, Boston.* We have reinvestigated the action of magnetic fields upon the eye. For stimulation we employed the core of an A.C. magnet, operated at frequencies of 5 to 90 cps, and at strengths up to 900 gauss. The only sensation evoked was that of flicker, which was maximal when the core was closely applied to the eye. No sensation could be elicited from the occipital region. The sensation is a colorless flicker, maximal in the periphery of the visual field, which varies in strength and frequency with the stimulus. When only a part of the retina is stimulated, the sensation elicited is noted only in the corresponding field of vision. With constant stimulation, the sensation vanishes in a number of seconds, more rapidly when the frequency is high and the intensity low. The sensation is prolonged by constantly moving the eyes. Recovery occurs in less than a minute. The sensation does not occur if pressure sufficient to abolish vision is applied to the eyes. The sensation is very similar to that evoked by passing sinusoidal currents (frequency, less than 100 cps) through the head. This, also, is maximal peripherally, colorless, prolonged by moving the eyeball,

abolished by orbital pressure, and subject to rapid fatigue.

Additional evidence on the afferent nervous factor in experimental traumatic shock. S. C. WANG. *Dept of Physiology, College of Physicians and Surgeons, Columbia Univ.* In dogs the mortality resulting from muscle trauma differs from that produced by a similar decrease in blood volume following simple hemorrhage (Fed. Proc., 4: 75, 1945). The residual blood volume at L.H. 50 (lethal hemorrhage at 50 per cent mortality) in muscle trauma series is 73 cc per kilogram body weight, whereas that in simple hemorrhage is 59 cc per kilogram. In animals with sublethal hemorrhage coupled with electrical stimulation of the cut central end of both sciatic nerves, the residual blood volume at L.H. 50 is raised to 69 cc per kilogram, which is significantly different from that in simple hemorrhage (Fed. Proc., 4: 54, 1945).

Thirty trauma experiments have now been completed on dogs in which chronic deafferentation of the hind-limbs had been carried out three to five weeks previously. In this series, the residual blood volume at L.H. 50 is 65 cc per kilogram, which is significantly lower than that found in the muscle trauma series mentioned above. Furthermore, the changes in heart rate and blood pressure as well as the degree of depression of sensorium produced by trauma are considerably modified by the previous deafferentation. Indeed the clinical course is in many ways similar to that seen in dogs subjected to simple hemorrhage.

These experiments indicate that the afferent nervous factor plays a definite role in contributing to the mortality of animals receiving muscle trauma. [Work done under contract with the Office of Scientific Research and Development.]

Some factors influencing the anaerobic glycolysis. CHARLES O. WARREN and FRANKLIN G. EBAUGH, JR. (by invitation). *Dept of Physiology and Anatomy, Cornell Univ. Medical College, New York City.* In comparing liver tumors with normal tissue, the question has arisen (Burk, Wisconsin Symposium on Respiratory Enzymes, 1942) as to the rate of anaerobic glycolysis of normal rat liver slices. Factors that influence this rate are consequently of interest. Other investigators have emphasized the importance of the duration of the experiment and the glycogen content of the liver. The present experiments deal with the effects of two media with a high content of potassium ions. One (Hastings and Buchanan, 1942) is a high-potassium bicarbonate medium and the other (Fuhrman and Crismon, 1944) a high-potassium phosphate medium. Both of these media yield higher values of $Q_G^{N_2}$ than the usual Ringer-bicarbonate medium, but still higher values are obtained by combining the salient features of both media, i.e. high potassium, bicarbonate and phos-

phate The $Q_{G}^{N_2}$ in this last medium is 5 to 10 times as great as in Ringer-bicarbonate medium Some of this difference is accounted for by the finding that a larger fraction of the glycogen which breaks down is recovered as lactic acid under these conditions So far, little or no utilization of added glucose has been found in any medium The experiments emphasize the importance of high concentrations of the three ions potassium, bicarbonate and phosphate in securing maximum activity of the liver glycolytic enzymes *in vitro* [Aided by a grant from the John and Mary R. Marille Foundation]

Reactions involved in insulin fibril formation DAVID F. WAUGH *Dept of Biology, Mass Inst of Tech, Cambridge* Seeding 0.1 ml fibrous insulin (JACS, 66:663, 1944) into 1.0 ml native insulin, both 2% protein at pH 1.6 and 25°C, shows the following: The initial weak flow double refraction increases until after 72 hrs strong static double refraction is present Approximately 50% of the native insulin now may no longer be recovered That native insulin has been converted to the fibrous form is demonstrated by measurements of double refraction and viscosity These effects are not obtained with native insulin at 25°C or fibrils diluted with acid At 100°C a seeded solution may become completely fibrous in a matter of three minutes while a comparable solution of native insulin requires ninety minutes

Data of this type are intercepted as follows: The initiation of a fibril (nucleus formation) and the subsequent elongation of the nucleus are to be considered separate reactions which normally proceed simultaneously

The two reactions may be separated experimentally: the elongation reaction by following fibril growth (chemical separation and measurement of fibril nitrogen) in a seeded solution near 25°C and nucleus formation by timing the first visible appearance of spherites near 100°C under conditions in which fibrils aggregate into spherites after reaching a minimum length, thus effectively removing them from solution The nucleus forming reaction generally appears as a second order reaction although it approaches first order at pH's near 1.0 Preliminary measurements indicate that elongation may be a first order reaction

Variability in the energy cost of standard exercises RAYMOND A. WEISS (by invitation) and PETER V. KARPOVICH *AAF School of Aviation Medicine, Randolph Field, Texas* Five selected exercises were given to 30 subjects The energy expenditure was measured by oxygen consumption using a closed circuit metabolism apparatus The energy cost of the exercises was expressed in terms of net oxygen consumption and also in multiples of the resting metabolic rate (cost in RMR)

The cost in RMR has an advantage over net oxygen consumption because the former has greater

independence from body size, and moreover introduces a convenient, easily understood measuring unit The reliability of the cost in RMR as obtained by the method of internal consistency was high, ranging from 0.86 to 0.90

Variations in energy cost between subjects for each exercise was found to be significantly large, which means that figures obtained for one subject cannot be accurately applied to other subjects

The cost in RMR was correlated with nine anthropometric measurements: length of arm and leg, girth of arm, forearm, thigh, and calf, height, weight, and surface area All correlations except one were low, showing that the variation in cost of exercise did not depend on the variations in body size

Effects of temperature gradients on the intensity, duration and thresholds of experimental traumatic pain HERBERT S. WELLS *Dept of Physiology, Univ of Minnesota, Minneapolis, Minnesota* Heat is commonly used to allay pain but its mechanism of action and degree of effectiveness require study

Moderate pain from clamping the finger web can be abolished by warming the clamp (and thence the clamped tissue) slowly to 37°C At higher temperatures pain reappears Rapid heating from any temperature may elicit pain Cooling the clamp below skin temperature causes pain, which is very severe, with wide radiation, if cooling is rapid With "adaptation" of hand and clamp to warm or cool water pain disappears, but returns if the clamp is cooled or warmed Pressure thresholds of pain may be altered two to four-fold by altering the temperature gradient between clamped and adjacent tissue

Percussion thresholds of "first" or "second" pain, produced by dropping a weight on the cool finger from graded heights, are elevated several fold by warming the skin to 37°C Brief recooling restores the low threshold state When the warm threshold stimulus is applied to the cool finger severe pain lasting many seconds results

Blood flow changes are not related directly to these phenomena, for similar findings obtain during occlusion Thermal effects on pain persist after "first" pain is abolished by prolonged occlusion

Since excitation of nerve requires energy transfers conditioned by potential differences (gradients) it is possible that thermal gradients excite pain fibers directly and sum with effects of mechanical or chemical potentials [Aided by a grant from the National Foundation for Infantile Paralysis, Inc.]

Effects of thermal gradients and thermal equalization on latent pain and hyperalgesia resulting from injury HERBERT S. WELLS *Dept of Physiology, Univ of Minnesota, Minneapolis, Minnesota* (Read by title) Mild injury of skin and

underlying tissues and of the nailbed was produced by percussion or by injection of iodine. Traumatic peri-arthritis was developed by prolonged clamping of interphalangeal joints. After pain had subsided, hyperalgesia remained (room temperature 20°C) and rubbing or pressing the area, or bending the joint, elicited soreness. Pain could be rekindled as effectively by cooling the skin over the part (sometimes by as little as 0.5°C) by immersion in water, exposure to cooler air, evaporation of water from the wetted surface, or by slight cooling of remote body surfaces to produce reflex drop in local skin temperature. Deep cooling of the part by prolonged immersion in water stopped the pain and lessened the degree of hyperalgesia to mechanical stimuli. Rapid warming, at various initial temperatures elicited pain also, while thermal equalization at 37°C was effective in lessening or abolishing hyperalgesia.

The more sensitive the injured area to mechanical stimuli, the more readily would small thermal gradients arouse pain. Conversely, the steeper the thermal gradient, short of that required for pain, the greater was the degree of hyperalgesia as tested by a standard mechanical stimulus, and the lower the mechanical threshold of pain. [Aided by a grant from the National Foundation for Infantile Paralysis, Inc.]

Liver function in malaria SAMUEL M. WELLS (by invitation), ANCEL KEIS, AUSTIN HENSCHEL, HENRY LONGSTREET TAYLOR and OLAF MICKELSEN (by invitation) *Laby of Physiological Hygiene, Univ of Minnesota, Minneapolis, Minnesota* (Read by title) Twelve men were inoculated with tertian malaria, which was terminated by quinine after 8 paroxysms, at an average of 69 hours of rectal temperature above 102°F. During and after the febrile period liver function was studied by means of the following tests: the prompt and total plasma bilirubin, the 5-milligram per kilogram bromsulfalein retention, the cephalin-cholesterol flocculation, the thymol turbidity, the two-hour urine urobilinogen, the Harrison test, and the methylene blue test for bilirubin in the urine. The bilirubin, urobilinogen, and bromsulfalein retention indicated deterioration of liver function during the febrile period, and prompt recovery afterward. The maximum values obtained were bilirubin, prompt, 0.45, and total, 2.58, milligrams per cent, urobilinogen, 22 milligrams per two hour period, bromsulfalein retention, 23% of injected material at 45 minutes. The cephalin-cholesterol flocculation became abnormal after about 7 days and remained abnormal for periods up to 17 weeks. The thymol turbidity reached a high value of 4 units on the fourth week from inoculation. No bilirubin was found in the urine at any time. Comparison of values for the plasma bilirubin obtained at the peaks of paroxysms showed that

after the initial rise there was wide fluctuation but no consistent trend, comparison of similar values for the bromsulfalein retention showed also wide fluctuation, but with slight trend toward progressive deterioration. The only significant relation of fever to the bilirubin and bromsulfalein retention was an average increase of 0.141 milligram per cent for the prompt bilirubin from the onsets to the peaks of the paroxysms. [This work was supported in part under contract with the Office of Scientific Research and Development. Support from other sources will be acknowledged in final publication.]

The mode of action of DDT J. H. WELSH and H. T. GORDON (by invitation) *Dept of Biology, Harvard Univ* DDT (2, 2-bis (p-chlorophenyl)-1, 1, 1-trichloroethane) has a similar, highly toxic action on insects and on Crustacea (shore crabs and crayfish) used in these studies. DDT acts on peripheral nerves, especially on fine nerve fibrils, and causes repetitive discharge. A single nerve impulse, on arriving at a DDT-treated region of a motor nerve axon, gives rise to a high-frequency volley of nerve impulses, and a tetanic contraction of the muscle results. The duration of the multiple-firing is longer when higher concentrations of DDT are applied, up to a maximum of several seconds, rhythmic spontaneous activity then occurs. Similar effects are produced by pyrethrins, veratrine and other unrelated compounds.

DDT also lowers the resting potential of nerve, and lowers the threshold to electrical stimulation.

Increasing the calcium-ion concentration in the environment of a DDT-treated nerve abolishes the DDT effects, but on returning to normal calcium the effects reappear. It is suggested that DDT is adsorbed in traces at or near the surface of the nerve axon and acts as a barrier-layer that hinders the normal interaction of calcium ions with the surface (e.g., calcium-linkage of cephalin molecules). The diversity of substances having similar effects indicates that the action is non-specific and physical rather than chemical. While this action appears to be the primary effect of DDT, other secondary changes may be of importance in causing the death of the organism. [The work done under a contract with the Office of Scientific Research and Development.]

Cardiovascular responses to explosive decompression W. V. WHITEHORN (by invitation), ABRAHAM EDELMAN (by invitation), and FRED A. HITCHCOCK *Laby of Aviation Physiology and Medicine, The Ohio State Univ Columbus* A technique has been developed by which the barometric pressure can be rapidly reduced, the rate and range of this reduction being controlled, (explosive decompression). Animals have been explosively decompressed at rates as fast as 650 ps² per second (10,000 to 50,000 ft in 0.02 seconds) without producing any serious consequences. Dogs

anesthetized with nembutal showed no significant change in the electrocardiogram or arterial blood pressure at rates up to 20 p.s.i. per second over ranges as great as from 10,000 to 50,000 ft. At rates greater than this a significant drop in blood pressure occurred. The extent of this drop was proportional to the rate and range of the explosive decompression. The blood pressure drop began two or three heart beats after the beginning of the decompression and the return to normal occurred within one minute. At decompression rates of 260 p.s.i. per second over ranges of 10,000 ft. to 50,000 ft. the drop in blood pressure was accompanied by bradycardia of vagal origin. Electrocardiograms were otherwise normal.

The primary cause of the blood pressure drop is believed to be interference with venous return by pulmonary distension and increased intrathoracic pressure produced when the rate of decompression exceeds the rate at which air can leave the lungs. This view is supported by the fact that interference with the flow of air from the lungs increased the extent of the blood pressure drop. Reflexes from distended abdominal viscera are probably also involved. [Work done under contract with the Office of Scientific Research and Development.]

Portal pressure gradients in hemorrhagic shock
CARL J. WIGGERS, DAVID F. OPDYKE and J. RAYMOND JOHNSON. *Dept. of Physiology, Western Reserve Univ. Medical School, Cleveland, Ohio.* Pressures were recorded in the aorta, portal vein, and inferior vena cava by calibrated optical manometers. By deducing changes in flow from estimates of cardiac output in similar previous experiments, changes of pressure gradients permitted conclusions regarding directional changes of resistance in mesenteric tributaries and portal outflow channels. Relative resistances in mesenteric and portal vessels were inferred by comparing aorto-portal and portal-caval gradients.

Mean pressure in the portal vein averaged 12 mm Hg, that in the inferior vena cava, 6 mm. Hepatic resistance to portal flow averaged 1/3 that in mesenteric tributaries. Epinephrine caused a dominant increase in mesenteric resistance, followed—as the pressor effect waned—by dominant increase in hepatic resistance. Pitressin caused solely a tremendous augmentation of mesenteric resistance. Histamine induced both a reduction in mesenteric and an increase in hepatic resistance.

Hemorrhagic hypotension was produced at 50 mm and 30 mm Hg levels by standard bleeding, previously described. Hemorrhagic shock followed several hours after reinfusion of blood. Portal pressure after a temporary decline tended to return toward control values during the period of 50 mm hypotension, declined during the 30 mm Hg period, increased far above control values after reinfusion, and remained definitely above control

levels until arterial pressures had fallen to shock levels. Results suggest that portal flow through the liver is reduced to a greater extent than indicated by changes in systemic and portal pressures, it is also reduced by relative increase in portal resistance.

Continuous intravenous infusion of alkalinizing agents during impending hemorrhagic shock conditions
HAROLD C. WIGGERS and RAYMOND C. INGRAHAM. *Dept. of Physiology, College of Medicine, Univ. of Illinois, Chicago.* During the standardized 90 minute hemorrhagic hypotension period used in this laboratory, the transition from an impending to an irreversible shock state was seen in 77% of untreated control animals. A developing acidosis was manifest in each animal, though variable in its intensity. The question arose whether acidosis influences the rate of onset of the above transition. This may perhaps be partially answered by attempts to prevent acidosis from developing through the expedient of continuous intravenous administration of either Na Lactate (0.87 gram/kg) or NaHCO_3 (0.65 gram/kg) throughout the entire hypotension.

The Lactate did not prove to be an effective anti-acidotic agent under those conditions, furthermore, 5 of 6 dogs entered irreversible shock during the hypotension period (Mortality, 87%). It did not reduce the number of animals entering irreversible shock before terminating the hypotension period by reinfusion of withdrawn blood.

NaHCO_3 treatment, however, resulted in maintenance of control or above control plasma CO_2 capacity in 7 dogs which recovered completely, as well as in several which died in shock. Mortality dropped to 47 percent in this series. Had the existence of acidosis in the others been recognized, it might have been possible to prevent the transition in many of the latter and thus to further decrease the mortality ratio by incrementing the amount of NaHCO_3 infused.

The conclusion is reached that in many instances, acidosis hastens the onset of irreversible conditions and that this action can usually be retarded by the infusion of proper amounts of NaHCO_3 to annul the effects of acidosis.

The permeability of the placenta to radioactive ions
WALTER S. WILDE, DEAN B. COWIE (by invitation) and LOUIS B. FLEXNER. *Dept. of Embryology, Baltimore, and Dept. of Terrestrial Magnetism, Washington, Carnegie Inst. of Washington.* We are now studying the rate of transfer of various radioactive ions across the guinea pig's placenta which belongs to the same morphological group (hemochorial) as that of man. It is our purpose to describe the permeability of this placenta with respect to charge and valence of ion at different stages of gestation. As with radioactive sodium (Flexner and Pohl, *Am. J. Physiol.* 132: 594), the

permeability to HPO_4 ion tagged with radioactive P increases as gestation proceeds, about 13 times more inorganic phosphate is transferred to the fetus across a unit weight of placenta near term (67 days) than at a gestation age of 30 days

The relative permeability of the placenta to different radioactive ions can be calculated from the activities measured in the maternal plasma and in the corresponding fetus. It is simply necessary to reduce the measured activity in a unit volume of maternal plasma to the same unit of activity for all the ions considered and to divide the activity measured in the fetus by the same factor. In this way it has been shown that the ratio, permeability to HPO_4 permeability to Na for a unit weight of the guinea pig's placenta is as follows: at the 30th day of gestation, 1.4, at the 53d day, 3.4, at the 64th day, 3.0. This is opposite in direction to the relative mobilities of the ions HPO_4 and Na in water (Boyle and Conway, *J. Physiol.* 100: 1).

Physiological effects of high negative mask pressures during simulated free-fall. J. W. WILSON (by invitation), F. G. HALL, and H. G. SWANN, *Aero Medical Lab., Air Technical Service Command, Wright Field, Dayton, Ohio*. There are indications from well known physical laws and from special experiments carried out with dummy setups in the wind tunnel that considerable suction (negative pressures relative to ambient pressure) may be developed at the end of the inspiratory tube of a pressure-breathing oxygen mask when an individual free-falls from an airplane. Consequently, experiments were conducted in which simulated free-falls were carried out from approximately 42,000 feet to determine whether the maximal suction expected during such a descent would seriously interfere with the breathing of individuals using a pressure-demand oxygen mask (A-13) and a high pressure emergency oxygen cylinder (H-2).

The arterial saturation of each subject was measured by the Millikan oximeter before and during the free-fall. The negative pressures developed in the mask during inspiration were measured throughout the descent by use of a glass spoon manometer mounted for photographic recording. From data on the rate of free-fall obtained by use of radar equipment and from wind tunnel tests with dummies, it was estimated that the maximal suction within the mask cavity during a free-fall would be approximately one inch of Hg.

Five individuals, subjected to negative mask pressures of one inch of Hg during simulated free-falls from 42,000 feet, successfully made the descents and without any after effects. A sixth individual, after one abortive start in which he complained of "not getting any air," made the descent successfully on a second trial. It was thus

indicated that the mask suction encountered during a free-fall are not incapacitating.

The nociceptive contraction of the musculus cutaneous maximus in the guinea pig as elicited by radiant thermal skin stimulation, temporal and spatial summation and susceptibility to centrally acting analgetic drugs. C. V. WINDER, C. C. PFIFFER (by invitation) and G. L. MAISON, *Research Dept., Parke, Davis and Co., and Dept. of Physiology, Wayne Univ., Detroit*. Radiant thermal stimulation of the depilated dorsallumbar skin of the guinea pig elicits a longitudinal, twitchy contraction of the skin. Increasing stimulation causes characteristic defense-withdrawal "radiation" of response. Threshold intensity approaches within fewfold of blistering intensity, further bearing on its noxious character.

The intensity-duration relationship for threshold stimulation agreed in general with that published for human pain perception with similar stimulation. The relative intensity-duration relationship was independent of area of stimulation, a small but real relative spatial summation (area) was independent of duration (temporal summation). An over 80 per cent "occlusion" was calculated and is considered related to poor local sign and the nociceptive nature of the stimulus-response.

Saline controlled intraperitoneal injection of morphine caused 80% elevation of threshold with time characteristics as expected, and essentially independent of general neuro-muscular or narcotic action. Ethyl 1-methyl-4-phenylpiperidine-4-carboxylate ("Demerol") and acetylsalicylic acid caused earlier, briefer elevations, in intensities and at doses in general agreement with known potencies relative to morphine, and essentially independent of observable general effects.

The intensity-threshold was rendered less susceptible to morphine when a very small area ($3 \pm \text{mm}^2$ instead of 730) or long duration (8 sec instead of 4) of stimulation was employed. This is interpreted as a decreased relative availability of higher-level spatial facilitation as morphine "substrate".

It is concluded that we deal with a conveniently elicited nociceptive mechanism with an important long-circuiting component through higher-level centers, of value in studying objective aspects of pain and pharmacological analgesia.

Brain structure after intermittent exposure to simulated high altitudes. W. F. WINDLE and A. V. JENSEN (by invitation), *Inst. of Neurology, Northwestern Univ. Medical School, Chicago*. Guinea pigs were subjected to an altitude pressure simulating 23,000 feet 6 hours daily 6 days weekly until they had accumulated 100, 200, 300 and 500 hours. Experimental animals and controls were sacrificed under nembutal by perfusing the vascular system

with formalin to fix the nervous system in situ. Every tenth serial brain section was stained by a controlled thionin technique. Other sections were prepared by methods for myelin sheaths and axis cylinders. Detailed comparison of experimental and control material revealed no hemorrhages, vascular changes or glia proliferations. No alterations in nerve cells and no reduction in their number could be detected. No changes in nerve fibers were observed.

Other guinea pigs intermittently subjected to 23,000 feet for 100 hours and then to 30,000 feet for another 100 hours showed no overt symptoms of brain injury. Each of four animals studied histologically had focal areas of anemic softening in the cerebellum. There were no hemorrhages and no generalized cytopathology was observed. Similar results were less consistently encountered after subjection to 30,000 feet for 100-150 hours intermittently. [Aided by a grant from The National Foundation for Infantile Paralysis, Inc.]

The retention and excretion of continuously administered intravenous salt solutions in man. A. V. WOLF (introduced by H. E. Himwich). *Dept. of Physiology and Pharmacology, Albany Medical College, Albany, N. Y.* When NaCl solutions are infused intravenously at constant rate (7 cc/min for 7 hours) the urinary concentrations of Na and of Cl, as well as the cc of urine formed per minute, approach steady state values which are calculable by the following equation of steady state (uncorrected for insensible water loss)

$$\frac{u}{i} = \frac{(A_T)_{Na} - I_{Na}}{(A_T)_{Na} - U_{Na}} = \frac{(A_T)_{Cl} - I_{Cl}}{(A_T)_{Cl} - U_{Cl}}$$

where u and i are the cc/min of urine and intake flow respectively, U and I are the respective urine and intake fluid concentrations of Na or of Cl, and A_T is the threshold of retention (normal plasma concentration of Na or of Cl).

When NaCl is infused the limiting isorrheic concentrations for Na and for Cl are equal (ca. 290 m eq/l), and the minimal isorrheic concentrations for Na and for Cl are also equal (ca. 20 m eq/l). The concentrations of Na and of Cl when they are between these critical concentrations, assume values which satisfy equation (1) to the extent of constituting supporting evidence for its validity.

Voluntary (self-protective) maneuvers which can be used to increase man's tolerance to positive acceleration (motion picture). E. H. WOOD and G. A. HALLFAXBECK (introduced by C. F. Code). *Acceleration Lab., Mayo Aero Medical Unit, Rochester, Minnesota.* Systolic blood pressure is a most important factor in determining man's tolerance to sudden exposure to high positive accelerations in the sitting position. Exposure to 5 g for a duration greater than the symptom

latent period of the retina or cerebrum to acute ischemic anoxia (3-10 seconds) usually produces blackout or unconsciousness. At this acceleration due to the height of the brain above the heart a systolic pressure of 120 mm of mercury at heart level affords a systolic pressure of only 5 mm of mercury at brain level and symptoms therefore result.

It has been found that voluntary maneuvers producing a temporary hypertension and aiding venous return will enable many individuals to maintain vision at 9 g. These maneuvers utilize either the pressor effect attained by coordinating muscular straining with a type of forced respiration or self-induced pressor reflexes such as occur immediately after a Valsalva maneuver of ten seconds' duration. Blackout prevention to 8 g by one such maneuver (M-1) is illustrated. This maneuver is described to pilots as follows: "Just before the g comes on with all your strength pull your chin in and your shoulders up. Simultaneously push your belly against a tightly drawn safety belt as if straining at stool. As you do this, yell the word 'Hey' as continuously as possible. Use up nearly all your breath on each 'Hey', then take a breath as quickly as possible and immediately start yelling again. Keep this up as long as you hold the g." [Work done under contracts with (1) United States Army Air Forces, Wright Field, Dayton, Ohio, and (2) the Office of Scientific Research and Development, National Research Council, Washington, D. C.]

The effect of anti-blackout suits on blood pressure changes produced on the human centrifuge. E. H. WOOD and E. H. LAMBERT. *Acceleration Lab., Mayo Aero Medical Unit, Rochester, Minnesota.* Direct arterial pressure (radial artery) was recorded in thirteen men during exposure to positive acceleration with and without anti-blackout suit protection. The procedures used are described in another abstract (see Lambert and Wood).

At the level of the eyes the decrease in blood pressure per g increase in acceleration averaged 32 mm Hg systolic and 19 mm Hg diastolic without the suit and 20 and 14 mm Hg respectively with the suit. At heart level with onset of acceleration, the pressures decreased on the average without the suit 30 mm Hg systolic and 00 mm Hg diastolic per delta g, while with the suit these pressures increased 50 mm Hg per delta g.

The anti-blackout suit increased g tolerance by 1.4 g, 1.5 g, 1.7 g and 1.7 g as determined by visual symptoms, blood content of the ear, ear pulse and blood pressure at eye level, respectively. The protection afforded blood pressure was significantly greater than that afforded vision ($P < 0.001$). This was associated with a tendency for visual symptoms to occur at higher

levels of blood pressure with the suit than without it

Inflation of anti-blackout suits produces an increase in blood pressure at heart level which is most marked during exposure to positive acceleration. This effect is responsible for the increased g tolerance produced. [Work done under contracts with (1) United States Army Air Forces, Wright Field, Dayton, Ohio, and (2) the Office of Scientific Research and Development, National Research Council, Washington, D C]

Electrical responses in gyrus cinguli evoked by electrical stimulation of ipsilateral mammillary body in cat and monkey. CLINTON N WOOLSEY, FRANCIS M DICK (by invitation) and ROBERT H FRANTZ (by invitation) *Dept of Physiology, Johns Hopkins Univ, School of Medicine, Baltimore 5, Md* (Read by title) The medial wall of one hemisphere and one mammillary body were exposed by careful removal of all neural tissue of the opposite side down to the level of the pons. Fine electrodes, 1 mm apart, insulated to the tips, were used to conduct single condenser discharges to the medial and interior parts of the mammillary body. For each point stimulated the cortical area of response was defined and cortical records were taken at points 2 mm apart along rectangular coordinates.

In cats two cortical areas of response were found: one above the posterior half of the corpus callosum. This extended around the splenium posteriorly and into the visual area superiorly. Often this area alone was activated and it always gave largest responses with shortest latencies. The second area of response occupies the medial surface of the frontal lobe, below the level of the corpus callosum. Here records showed a small early surface positive wave and a later slower component. The slower component never occurred without response in the retrosplenial area. Latency relations and a surface negative wave above the anterior corpus callosum suggested that the retrosplenial area relayed to the rostral area. In monkey, only the retrosplenial area (areas 23 and 29, Bailey et al *J Neurophysiol*, 1944) could be activated. The pathway out of the mammillary body is the mammillothalamic tract.

The study demonstrates by electrical methods projection of the mammillary body to the gyrus cinguli.

Comparative studies on dual somatic afferent areas in cerebral cortex of rabbit, cat, dog, pig, sheep and monkey. CLINTON N WOOLSEY *Dept of Physiology, Johns Hopkins Univ, School of Medicine, Baltimore, 5, Md*. It is generally considered that each main afferent system has one "primary" pathway into the cerebral cortex. Oscillographic studies show that there are at least two somatic (Adrian), visual (Talbot) and auditory areas (Woolsey and Walzl). These are termed provisionally: somatic, visual and auditory areas

I and II. Areas I correspond to classical "primary" receiving areas, each area II was "second" in time of discovery.

Somatic area I (postcentral homologue) is strictly *contralateral* in relation to skin, except for part of the face area which is ipsilateral and present in all species studied. Somatic I varies from species to species in development of its various subdivisions, apparently according to specialization of peripheral receptor surfaces.

Somatic area II (Adrian's "second") lies on the superior bank of the sylvian fissure in monkey, in the anterior ectosylvian gyrus of carnivores and ungulates, in *Par 5* (Rose) of rabbit. It is *bilateral* in relation to skin, receiving impulses from all parts of the body surface, largest responses are from snout, limb apices and tail. Differentiation within somatic II increases from rabbit to monkey but does not parallel that of somatic I. Face areas I and II are contiguous.

Existence of dual areas for each major sensory system suggests a fundamental principle of neural organization which apparently is not limited to cerebral cortex (Cf Snider and Stowell on cerebellum), and may extend to the peripheral nervous system.

Further studies of cortical and retinal influences upon vestibulo-ocular reflexes. H T WYDIS (by invitation) and E A SPIEGEL *Dept of Exp Neurology, Temple Univ Medical School, Philadelphia, Pa*. Continuing our previous experiments on the effect of cerebral lobectomies upon postrotatory nystagmus (Wydis and Spiegel, *Fed Proc* 4:79, 1945), we compared the effect of partial lesions of the frontal and the occipital lobes with that of complete lobectomies upon the excitability of the vestibulo-ocular reflex arc in dogs and cats. Furthermore retinal impulses were eliminated by transection of both optic nerves, and this operation was combined with lobectomies. Following the bilateral optic nerve section, the duration of the postrotatory nystagmus was increased to 2-3 times and the number of jerks to 1.4-7 times the preoperative values. In this stage of increased reactivity of the vestibulo-ocular reflex arc, some dogs displayed a pronounced "after-after" discharge following labyrinthine stimulation by turning, the rotation being followed first by a nystagmus in the opposite direction and then one beating in the direction of rotation. Occipital lobectomy in these dogs with cut optic nerves failed to produce the directional preponderance to the side of the lobectomy usually appearing in normal dogs after this operation. It is inferred that the increased reactivity of the vestibulo-ocular reflex arc following occipital lobectomy is due to a release of this system from an inhibitory mechanism originating in the retinas.

Correlation of electrical and mechanical events

in the intestinal lumen of unanesthetized dogs W B YOUMANS and LYNN FOLTZ (by invitation) *Univ of Oregon Medical School, Dept of Physiology, Portland* Simultaneous oscilloscopic records were obtained of the changes in the potential of the mucosa and of changes in pressure within the lumen of Thiry jejunal fistulae in unanesthetized dogs

Records were obtained during rhythmic activity and during moderate distention The effects of adrenalin, atropine, physostigmin, and choline derivatives were studied

There is a slow smooth potential change which begins $8 \text{ second} \pm 4 \text{ second}$ prior to the beginning of the increase in pressure associated with each rhythmic contraction There are numerous medium fast potentials confined to the period of rising pressure The latter are accentuated by choline derivatives and physostigmin and are eliminated by atropine and adrenalin even though the slow smooth rhythmic potentials persist in modified form The findings will be compared with those of Puestow, of Berkson, and of Bozler and others who used different recording devices and different experimental preparations The medium fast waves are interpreted, in agreement with Bozler, as smooth muscle action potentials The source and mechanism of production of the slow rhythmic potential changes remains unknown

If the intestine is distended, by procedures identical with those used to elicit the intestino-intestinal inhibitory reflex, a burst of very fast small potentials, having the same characteristics as those recorded from sympathetic ganglia, is initiated When the distention is removed these potentials gradually become less frequent so that soon discrete spikes are seen These are interpreted as action potentials in nerve fibers lying close to the mucosal surface

The passage of endogenous estrogen across the parabiotic union in rats ISOLDE T ZECKWER *Univ of Pennsylvania Medical School* In former experiments (Arch Path 38 99, 1942) the author described changes in the pituitary, ovaries and mammary glands in rats united in parabiosis with ovariectomized rats for many months During the first 2 weeks when FSH from the pituitary of the ovariectomized rat A passes to the intact rat B stimulating the ovaries of B to secrete estrogen, the vagina of B becomes cornified and that of A atrophic In the present experiments, histological sections show that during the next month when estrogen stimulates the pituitary of B to release LH with consequent formation of many large corpora lutea, the state of the vagina of B changes from cornification to mucification, and the vagina of A becomes cornified Thus apparently with excessive luteinization in B, estrogen is raised to such a level

that it can pass to A, whereas in B, progesterin over-balances estrogen in its effect on the vagina and results merely in mucification Subsequently, fluctuating estrus in B, noted by others, suggests that estrogen reaching A modifies the secretion of FSH by the pituitary of A Mammary glands remain atrophic in A, indicating that the castrate pituitary, even when estrogen is circulating in A, does not release mammotropic factors After 6 weeks the pituitary of B is exhausted of LH, all corpora lutea disappear and then occur the changes previously described dependent upon continuous presence of estrogen in B and its absence in A These data amplify the findings of previous workers

Studies on spontaneous hemostasis, with evidence for a humoral factor MARJORIE B ZUCKER (introduced by M I Gregerson) *Dept of Physiology, College of Physicians and Surgeons, Columbia Univ* (Read by title) Non muscular venules in the mesoappendix of nembutalized rats were observed microscopically before and after transection A platelet thrombus formed at each stump and bleeding stopped within 4 minutes (average), without evidence of vasoconstriction Bleeding usually recurred, often repeatedly, through or around the thrombus for periods up to 75 minutes In similar experiments on rats with thrombocytopenic purpura produced by anti-platelet serum, no thrombus was seen, and bleeding was continuous until death

When muscular mesenteric veins were nicked, marked local venous constriction occurred within 15 seconds, followed by the formation of a white thrombus When bleeding ceased (2 minutes average), local constriction of the artery accompanying the vein was usually evident opposite the thrombus In 6 experiments, bleeding ceased permanently, in 8 it recurred briefly once or twice and in 2 cases it was renewed for long periods One week after splanchnic nerve section hemostasis was normal In thrombocytopenic rats, no thrombus or local arterial contraction was seen, despite venous constriction, bleeding continued uninterrupted Heparitized rats (500 to 2250 units/kg) usually formed thrombi but continued to bleed

Thus, platelet thrombi are essential to hemostasis Local venous constriction occurs in muscular vessels, probably partly the result of mechanical stimulation of smooth muscle Vasoconstriction may be responsible for the lower incidence of renewed bleeding in these as compared with non-muscular vessels The local arterial constriction which occurs only near the thrombus, as well as part of the venous contraction, is probably a response to the vasoconstrictor substances in the blood platelets [Aided by a grant from the Baruch Committee on Physical Medicine to Columbia Univ]

THE AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS

THIRTY-SEVENTH ANNUAL MEETING

Atlantic City, N J , March 11, 12, 13, 14, 15, 1940

(For possible corrections in any of the following abstracts see the next issue)

Effect of carbohydrate feeding on the urinary output of amino acid and other metabolites in man. ANTHONY A. ALBANESE AND VIRGINIA IRBY and JANE E. FRANKSTON (by invitation) *Dept of Pediatrics, New York Univ College of Medicine* The long known and well confirmed observation that extra carbohydrate administration induces N and urea retention in man and experimental animals suggested the undertaking of a study on the effect of supplementary carbohydrate feeding on the urinary output of amino acid and other metabolites. Experiments on this point yielded the following findings:

Administration of 25 gm of glucose or sucrose within an hour of a standard breakfast to each of 3 adult subjects was observed to consistently lower the urinary N output by 150 ± 50 mg for the ensuing 3 hour period as compared to a normal baseline value. Analyses of these specimens disclosed the N-retention to be reflected principally in a decreased urea excretion and to a lesser degree in a drop of the amino N, creatinine, creatine and arginine levels. Measurements of the phenylalanine, histidine, total S, indican, methionine, cystine and total phenol output showed no significant correlative variations. Following carbohydrate ingestion, the excretion of tryptophane of one subject (male) regularly fell to zero from a normal of 12 mg for the period, whereas in the other two subjects (females) the output of this metabolite was decreased less abruptly and regularly subsequent to the sugar feeding.

Supplementary experiments demonstrated that (a) ingestion of 50 gm instead of 25 gm of the sugars did not augment N and urea retention or alter appreciably the output of other metabolites from the 25 gm intake level, (b) the N retention effect of supplementary carbohydrate feeding is adversely affected, and can even be abolished, by abnormal urine volumes, and (c) ingestion of 25 gm of L-arabinose failed to induce N, or urea retention.

Estimation and characterization of bound amino N of normal human urine. ANTHONY A. ALBANESE, L. EMMETT HOLT, JR., JANE E. FRANKSTON (by invitation) and VIRGINIA IRBY (by invitation) *Dept of Pediatrics, New York Univ College of Medicine* An estimation and characterization of the bound amino acids in human urine would be of value in the correlation of excretion patterns in dietary amino acid deficiencies and perversions of protein metabolism. To facilitate

evaluation of bound amino N in the abnormal, a study of the characteristics of this fraction in the normal human was undertaken.

Aliquots of 24-hour protein-free urine specimens from 10 adults on normal diets were submitted to amino acid analyses prior and subsequent to a 24 hour hydrolysis under reflux with 6N HCl. This treatment was found to increase the average amino N from 170 ± 56 mg to 588 ± 217 mg or 3.8 ± 0.9 to 11.6 ± 1.6 per cent amino N of the total N. These data indicate that 70 per cent of the total urinary amino acids occur in a bound form. The increment in amino N so obtained was characterized by an increase of the average daily methionine value from 188 mg to 461 mg, of cystine from 49 mg to 80 mg, and hydroxyamino N from 16 to 108 mg. Since the chromogenic groups of arginine, histidine and tyrosine are known to yield colors even in whole proteins, as might be expected, the figures for these amino acids were not altered appreciably by the hydrolysis. An erratic but consistent decrement observed in the phenylalanine value subsequent to hydrolysis was found to be due to destruction of this amino acid. Hydrolysis of urines in the presence of 10 per cent barium hydroxide failed to augment the tryptophane content.

The in vivo inactivation of brain cytochrome oxidase and its effect on glycolysis and on high energy phosphorus reservoirs in brain. HARRY G. ALBAUM (by invitation), JAY TEPPERMAN (by invitation) and OSCAR BODANSKY *Chemical Warfare Service, Edgewood Arsenal, Md* In an attempt to elucidate the mechanism of cyanide poisoning in intact animals, rats were injected with sodium cyanide intraperitoneally (5 mg/kg) and studies made on brain cytochrome oxidase activity and on a number of intermediates in carbohydrate metabolism. In tests on cytochrome oxidase activity, brains were removed between 3½ and 8 minutes after injection, homogenized in a Waring blender and the enzyme activity determined spectrophotometrically from the rate of oxidation of cytochrome C. Carbohydrate intermediary compounds were determined on control and experimental animals by placing both under nembutal anaesthesia (50 mg/kg) and injecting cyanide after ten minutes. After four additional minutes both groups of animals were killed by immersion in liquid nitrogen. Brains were removed while the animals were still frozen and the following determined: glycogen, lactic acid, inorganic phosphate,

adenosine triphosphate, adenosine diphosphate, phosphocreatine, fructose, diphosphate, phosphopyruvate and phosphoglycerate

Rats treated as above showed a 50 per cent diminution in brain cytochrome oxidase activity, decrease in glycogen, and increases in inorganic phosphate, lactic acid, hexose diphosphate, phosphoglycerate and phosphopyruvate. These changes show a shift to anaerobic metabolism. The decrease in phosphocreatine and adenosinetriphosphate and the increase in adenosinediphosphate indicate that energy derived from these glycolytic processes is inadequate to maintain the high energy phosphorus reservoir of the cell at a normal level. These observations suggest that in the brain the maintenance of the high energy phosphorus reservoirs is dependent upon aerobic processes mediated largely through the cytochrome oxidase system.

The relationship between cytochrome oxidase and succinic dehydrogenase in the developing chick embryo. HARRY G. ALBAUM, ALEX B. NOVIKOFF, and MAURICE OGUR (introduced by Elvin A. Kabat). *Brooklyn College, Brooklyn, N. Y.* Succinic dehydrogenase and cytochrome oxidase generally occur together in animal tissues, and both are presumed to be associated with macromolecular entities. The present study was undertaken to determine whether changes in the concentration of cytochrome oxidase during the development of the chick, previously reported by one of the authors, are paralleled by corresponding changes in succinic dehydrogenase concentration.

A varying number of embryos of approximately the same age (determined by examination of the embryos) were homogenized in a small quantity of cold distilled water, and the homogenates analyzed for both enzymes. The embryos analyzed ranged in average age from 32 hours to 11 days. Enzyme activity was determined in the Warburg at 37°C, using ascorbic acid as a substrate for cytochrome oxidase and sodium succinate for succinic dehydrogenase.

By this method of analysis, the succinic dehydrogenase activity can not be reliably determined until the second day, but even the earliest embryos gives consistent data for cytochrome oxidase activity.

The relationship of the two enzymes can best be expressed in terms of the ratio

$$\frac{\text{cytochrome oxidase activity}}{\text{succinic dehydrogenase activity}}$$

This ratio is high at two days, decreases until the fifth day, and then remains at a fairly constant level through the eleventh day.

Thus, changes in cytochrome oxidase concentration are not paralleled by changes in succinic dehydrogenase concentration until the fifth day of development.

Some properties of lysozyme. GORDON ALBERTON (by invitation), H. L. FEVOLD, and H. D. LIGHTBODY. *Western Regional Research Lab., Albany, Calif.* Lysozyme is inactivated by reagents which attack the reactive protein groups. Formaldehyde, benzoyl chloride, or phenylisocyanate in alkaline solution or formaldehyde in gaseous form completely inactivates the purified lysozyme, as does nitrous acid. Methylation by solution in methyl alcohol acidified with hydrochloric acid results in complete inactivation also. Reagents such as acetic anhydride, acetic anhydride plus pyridine, acetyl chloride, benzoyl chloride, or phenylisocyanate do not react with lysozyme under anhydrous conditions at 25°C, as indicated by unchanged solubility and bacteriolytic activity.

Lysozyme has been found to be rather stable in solutions over the pH range of 3 to 11 at 23°C. After three months no loss of activity had taken place at pH 9.0 or below and only 25 per cent loss was found at pH 10 and 11. At pH 12, 60 per cent loss took place in 7 days.

The reported inactivation with iodine and reactivation with sulfite (Meyer, K., et al., *J. Biol. Chem.*, 113, 303, 1936) has been confirmed. In no case, however, has inactivation with iodine been complete nor has reactivation been complete.

Analysis of the pure lysozyme showed that it is composed of 48.7 per cent carbon, 6.74 per cent hydrogen, 17.5 per cent N, 2.3 per cent sulfur, and (by difference) 24.8 per cent O.

Metabolism of cinchonine in dogs and man. JAMES C. ANDREWS and W. E. CORNATZER (by invitation). *Dept. of Biological Chemistry and Nutrition, School of Medicine, Univ. of North Carolina, Chapel Hill.* Comparisons of the metabolic behaviour of cinchonine in dogs and in man have confirmed the conclusions of Haatt to the effect that in contradistinction to other common cinchona alkaloids, cinchonine, administered to human subjects, appears in the blood stream in such slight concentrations as to be hardly detectable. However when administered to dogs it produces blood concentrations of about the same order as do the other common cinchona alkaloids. Further comparisons in both dogs and human subjects were therefore made using carefully purified samples of the dihydrochlorides of quinine, cinchonidine and cinchonine. In two dogs with isolated intestinal loops, the rates of absorption of the three alkaloids were not markedly different and the resulting blood levels were about the same. The percentage urinary excretion of that portion of the drug absorbed from the loop was higher for both cinchonine and cinchonidine than for quinine. However, with normal human subjects, cinchonine differed

¹ Bureau of Agricultural and Industrial Chemistry Agricultural Research Administration U. S. Department of Agriculture

sharply in producing blood concentrations of less than one mgm per l. Its percentage urinary excretion was also lower. Other work has demonstrated that this result is not due to a lower rate of absorption in the human. [Supported by a grant from the Samuel S. Fels Fund.]

Mechanism of skeletal disuse atrophy W. D. ARMSTRONG, *Laby of Applied Biochemistry, Univ of Minnesota, Minneapolis*. The specific activity of the urinary phosphorus of rats, in the interval 9-14 weeks after subcutaneous administration of radioactive phosphorus, decreases so slowly as to afford a means of determining the specific activity of the plasma inorganic phosphorus. The phosphorus specific activity of the humeri of rats, 7 or more weeks after administration of radioactive phosphorus, is greater than that of the urine (and plasma) and decreases with time as was shown in experiments in which one arm was amputated three weeks before the animals were sacrificed. The phosphorus specific activities of the humeri of normal and paralyzed limbs of rats were found to be equal when unilateral brachial paralysis was produced 11 weeks after administration of radiophosphorus and three weeks before the animals were sacrificed. The exchange of phosphorus by the humeri of normal and paralyzed limbs for that of the blood was found to be equal in experiments in which bone formation was made a negligible factor by sacrifice of the animals within a few hours after administration of radiophosphorus. These results indicate that skeletal atrophy of paralyzed limbs is due primarily to increased bone resorption. [Supported by a grant from the Josiah Macy, Jr. Foundation.]

Skeletal atrophy from disuse W. D. ARMSTRONG, *Laby of Applied Biochemistry, Univ of Minnesota, Minneapolis*. Continuing work previously reported (*Fed. Proc.* 4, 81 (1945)), the following results have been obtained in experiments in which the nerves of the right brachial plexus of mature male rats were sectioned and the animals allowed to live 21 days following the operation. (a) Diets grossly deficient in calcium or phosphorus produced markedly reduced percentage of ash, fat-free and total ash weight of the humeri of the normal limbs. The mean atrophy of the paralyzed limbs was 36.8 and 31.2 per cent respectively for these two groups (13.7 per cent in a control group). (b) Enrichment of an adequate diet with calcium or with phosphorus produced no differences from the controls in the humeri of the normal or paralyzed limbs. (c) A diet grossly deficient in protein markedly reduced the amount of bone in both humeri. The atrophy of the paralyzed humeri was 29.6 per cent. The ash percentage of both humeri was increased. (d) Animals restricted to six grams per day of an adequate diet exhibited reduced fat-free and total ash weights of both humeri and

normal percentages of ash. The atrophy of the paralyzed limbs was 21.4 per cent. (e) Estradiol dipropionate (2.5 or 5 micrograms by subcutaneous injection on alternate days) increased the percentage of ash, fat-free and total ash content of the humeri and decreased the atrophy of the paralyzed limbs. [Supported by a grant from the Josiah Macy, Jr. Foundation.]

Activator for soybean lipoxidase A. K. BALLS, BERNARD AXELROD and MARIAN W. KIES (by invitation), *Bureau of Agricultural and Industrial Chemistry, U. S. Dept. of Agriculture, Albany, California*. The existence of a poorly defined material of wide occurrence capable of "activating" soybean lipoxidase was reported by us.¹ Cosby and Sumner² have since reported that, "Contrary to the findings of Balls, et al., our investigations have revealed no activator for lipoxidase."

We have repeated the experiments of these authors. The failure of Cosby and Sumner to find activator in soybeans, malt, etc., was due to the inclusion of gum arabic in their tests. Four different specimens of gum arabic tested by us were found to contain considerable activator. The quantity of gum used by Cosby and Sumner was sufficient to give full activation. Thus their system is unsuitable for demonstrating the activating effect of other materials, but if gum arabic is omitted therefrom, the activating effect of our preparations can be demonstrated.

Alcoholic fractionation of gum arabic enabled us to concentrate the "activator" tenfold. Like the soybean material, it was soluble in 60 but precipitated by 90 per cent ethanol.

Attention is called to our published opinion that the "activator" functions as a stabilizer, not as a coenzyme, for the quantity required for maximum activation does not depend on the amount of enzyme but on the amount of substrate present, thus explaining the unusual substrate optimum reported for this system.³

The oxidative pathway of pyruvate metabolism E. S. GUZMAN BARRON, GRANT R. BARTLETT (by invitation), and GEORGE KALNITSKY (by invitation), *Univ. of Chicago, Chicago*. Barron and Miller⁴ showed in 1932 that pyruvate is oxidized by gonococci into acetic acid and CO₂. This oxidative pathway has not yet been demonstrated in animals or plants, and the many schemes postulated to explain the metabolism of pyruvate by animal tissues have not considered its oxidation to acetic acid and CO₂. Of the different halogenated acids, fluoroacetate has been found to act as specific

¹ Balls, A. K., Axelrod, B., and Kies, M. W., *J. Biol. Chem.* 149: 491 (1943).

² Cosby, E. L., and Sumner, J. B., *Arch. Biochem.* 8: 259 (1945).

³ Sumner, J. B., and Sumner, R. J., *J. Biol. Chem.* 134: 531 (1940).

⁴ Barron, E. S. G., and Miller, P. C., *J. Biol. Chem.*

inhibitor of acetate metabolism it inhibits the oxidation of acetate by human and rat kidney cortex slices, by rat liver and heart slices, by bakers' yeast, and by *Corynebacterium creatinovorans*. It inhibits also the synthesis of carbohydrate and citrate from acetate by yeast, and *C. creatinovorans*, and the synthesis of carbohydrate by rat kidney slices. This inhibition is of the competitive type, for it can be partially reversed on addition of large amounts of acetate. When tissue slices (kidney, liver, heart) or yeast were incubated in the presence of pyruvate and fluoracetate, an accumulation of acetate was demonstrated by the specific lanthanum color reaction, in the absence of fluoracetate no acetate was found. This accumulated acetate was produced by the oxidation of pyruvate and by the inhibition of acetate oxidation by fluoracetate. Fluoracetate did not inhibit the dismutation, the reduction, or the decarboxylation of pyruvate nor did it have any effect on the oxidation of isocitrate, α ketoglutarate, malate, or succinate by their respective oxidase enzymes.

Ascorbic acid and tyrosine metabolism DANIEL H. BASINSKI (by invitation) and ROBERT R. SEALOCK, *Dept. of Vital Economics, Univ. of Rochester, Rochester*. In an attempt to determine the point of action of ascorbic acid in its previously described role in phenylalanine and tyrosine metabolism, selected derivatives and metabolic intermediates have been synthesized and fed to scorbutic guinea pigs with and without ascorbic acid supplementation. Each compound was selected in order to test specific and individual features of the structures of the two amino acids. Included were D-phenylalanine, D-tyrosine, phenylpyruvic acid, p-hydroxyphenylpyruvic acid, acetyl-1-phenylalanine, N-acetyl-1-tyrosine, diacetyl-1-tyrosine, p-methoxyphenylalanine, phenylaminobutyric acid and S-benzylcysteine. With the daily feeding of 2.76 millimols of each, the urinary excretion of α -keto acids, tyrosine phenols (tyrosyl value) and homogentisic acid was determined.

The results obtained indicate that each of the above compounds, with the exception of phenylpyruvic acid, is metabolized by the guinea pig without dependence upon an adequate intake of ascorbic acid. Phenylalanine, phenylpyruvic acid and 1-tyrosine proved to be the only compounds dependent upon sufficient ascorbic acid for their metabolism. It, therefore, may be concluded that the vitamin operates in the sequence of reactions involving these three compounds at a point prior to the formation of the tyrosine keto acid. It also seems certain that this metabolic activity of the vitamin is extremely specific with regard to the structural characteristics of the compound being metabolized.

Isolation and characterization of two antigenic fractions of proteus OX-19 AARON BENDICH (by invitation) and ERWIN CHARGAFF, *Dept. of Biochemistry, Columbia Univ.* Two antigens from *Proteus OX-19*, an organism known to be agglutinated by typhus convalescent sera, have been prepared and characterized in a variety of ways. The extraction of the micro-organisms with trichloroacetic acid (or, although this is less effective, their digestion with crystalline trypsin) yields two antigenic fractions, different in immunological specificity and in particle size, but rather similar in chemical composition. A heavy particulate fraction (C-2), sedimentable at high centrifugal speeds, is endowed with specificity to typhus sera as well as to *Proteus* antisera, a lighter fraction (C-11) possesses *Proteus* specificity only. Both fractions, which are homogeneous electrophoretically, are phosphorylated lipocarbohydrate-protein complexes. The typhus-reactive fraction C-2 loses its precipitability by typhus sera when heated or freed of lipids.

The study of the chemical composition of the antigens revealed them as complexes consisting of a) lipids (with a high proportion of free fatty acids), b) a protein or polypeptide (including arginine, lysine, glutamic acid, leucine, isoleucine, proline and phenylalanine, but free of histidine, tyrosine, and tryptophane), c) a polysaccharide (containing hexoses, viz., mannose, galactose, and perhaps glucose, and N-acetylglucosamine). Part of the organically bound phosphorus is present in the form of an extremely acid-labile linkage. In connection with the presentation of a modified method for the estimation of amino sugar, the evidence for the occurrence in these antigens of N-acetylglucosamine containing phosphoric acid in ester linkage is discussed. A method for the quantitative determination of acetyl groups by means of isotope dilution is likewise presented. [Work done under contract with the Office of Scientific Research and Development.]

Kinetics of the iodination of tyrosine LOUIS BERGER (by invitation) and PHILIP A. SHAFFER, *Dept. of Biological Chemistry, Washington Univ. School of Medicine, St. Louis*. The rate of the reaction,

$\text{Tyrosine} + 2\text{I}^- \rightarrow 2,6\text{-Diiodotyrosine} + 2\text{HI}$, (1) is described by a bimolecular equation. The rate of the reaction is inversely proportional to $[\text{H}^+]$ and to the square of $[\text{I}^-]$, and directly proportional to the buffer concentration, confirming the work of Li, [J. Amer. Chem. Soc., 66: 228 (1944)].

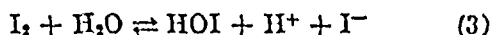
All buffers are not equally effective, and in general the rate is a function of the dissociation constant of the buffer and of the number of charges borne by the components of the buffer system. These buffer effects are not accounted for by variation of ionic strength, but conform with

Bronsted's analysis of buffer catalysis [*Z. physikal Chem*, 108 185 (1924)]

The effects of $[H^+]$ and $[I^-]$ are explainable on the assumption that $HIOI$ rather than I_2 is the primary iodinating agent. Increasing the $[H^+]$ or the $[I^-]$ decreases the amount of $HIOI$ resulting from the following equilibrium reactions



and



which are known to exist in aqueous solutions of I_2 .

The effect of buffer concentration on the rate of reaction (1) is also explained on the basis that $HIOI$ is the iodinating agent since it has been found that increasing the buffer concentration increases the equilibrium constant of reaction (3), i.e., increases the $[HOI]$ present at equilibrium.

The observed temperature coefficient of reaction (1) ($Q_{10} \pm 4.0$) is slightly lower than the temperature coefficient expected from calculations involving only variations of $[HOI]$ with temperature. It appears, therefore, that the iodination of tyrosine by HOI has a negative temperature coefficient.

On the formation of acetylcholine by choline acetylase in the nerve axon M. BERMAN and D. NACHMANSOHN (introduced by H. T. Clarke) *College of Physicians and Surgeons, Columbia Univ., New York*. The high concentration of a specific cholinesterase in the nerve axon is one of the essential facts in favor of the concept that the release of acetylcholine is an intracellular process associated with the nerve action potential. The presence of a specific and highly active enzyme mechanism indicates that the ester may be metabolized there at a high rate. It suggests the possibility that acetylcholine may be formed in the axon as well as at synaptic regions.

As shown by Nachmansohn and Machado, acetylcholine is formed by choline acetylase, an enzyme system extracted from brain but not found in other organs. This enzyme forms acetylcholine in cell free solution in the presence of adenosine triphosphate under strictly anaerobic conditions. Formation of acetylcholine by choline acetylase has been demonstrated in the axon as well as at the synapse. 1 gram of rabbit sciatic forms 70 to 90 μ g of acetylcholine per gram per hour.

The interdependence of acetylcholine formation and function has been tested on degenerating rabbit sciatic 48 hours after section of the nerve when conductivity is still possible, the rate of formation has decreased by only 20 to 25 per cent. 72 hours after section, at a time when conductivity has disappeared, the loss of enzyme activity amounts to about 60 to 70 per cent.

The significance of the high rate of acetylcholine formation in the nerve axon by choline acetylase will be discussed in connection with recent criticism denying a correlation between acetylcholine metabolism and conductivity.

cism denying a correlation between acetylcholine metabolism and conductivity.

***l*-Hydroxy acid oxidase** M. BLANCHARD (by invitation), D. E. GREEN, V. NOCITO CARROLL (by invitation) and S. RATNER *Depts of Medicine and Biochemistry, College of Physicians and Surgeons, Columbia Univ.* The *l*-amino acid oxidase of rat kidney has been obtained in homogeneous state and shown to be a flavoprotein containing flavinmonophosphate as prosthetic group.¹ It has been observed that preparations of this enzyme are also capable of catalysing the oxidation of *l*-hydroxy acids to the corresponding keto acids and that the ratio of the two catalytic activities is constant from the first crude extracts to the final electrophoretically homogeneous flavoprotein. In presence of *l*-hydroxy acids the flavin groups of the enzyme are bleached rapidly just as by amino acids. Thirteen *l*-hydroxy acids have been tested and found to be oxidized in the following descending order of activity: the hydroxy acids corresponding to valine, α -aminobutyric acid, leucine, norleucine, phenylglycine, alanine, phenylalanine, methionine, histidine, serine, aspartic, glycine, and arginine. The hydroxy acids are oxidized much more rapidly than their amino acid counterparts. In presence of an *l*-hydroxy acid and an *l*-amino acid no summation of rates is observed. The enzymatic oxidation of hydroxy acids by molecular oxygen results in the formation of α -keto acids and hydrogen peroxide.

The *l*-hydroxy acid oxidase described above has been found only in association with *l*-amino acid oxidase activity and is not identical with the lactic or malic dehydrogenases which catalyze the oxidation of their substrates by diphosphopyridine nucleotide.

Acetylation of foreign amines by acetyl amino acids KONRAD BLOCH and D. RITTENBERG *Dept of Biochemistry, College of Physicians and Surgeons, Columbia Univ.* With the aid of deuterium, acetic acid has been shown to be an equally effective acetylating agent for α -amino acids (*l*- and *d*- γ -phenyl- α -amino butyric acid) and for the aromatic amines *p*-amino benzoic acid and sulfanilamide [*J. Biol. Chem.*, 159. 45 (1945)]. The acetyl derivatives of some natural amino acids are known to be deacetylated *in vivo*. In experiments to test the availability of such acetyl groups for the acetylation of foreign amines, the deuterioacetyl derivatives of glycine, *l*- and *d*-leucine, *l*-glutamic acid and *l*-alanine have been prepared. The acetyl derivative of phenyl-amino-butyric acid, but not of *p*-amino benzoic acid, excreted following administration of deuterio acetyl glycine or deuterio acetyl leucine, contains several times as much deuterium as that found after feeding of equivalent

¹ Blanchard, M., Green, D. E., Nocito-Carroll, V., and Ratner, S., *J. Biol. Chem.* 161 583 (1945).

amounts of deuterio acetic acid. Although with deuterio acetate the isotope concentration of excreted acetyl is directly proportional to the quantity of administered deuterioacetate, it is independent of the amount of administered acetyl glycine. These findings are interpreted to show that in the acetylation of phenylaminobutyric acid by acetyl derivatives of natural amino acids formation of free acetic acid may not be an intermediate step. The possibility that a transfer of acetyl radicals is involved will be discussed.

Separation of amino acids with the aid of ion exchangers. RICHARD J. BLOCK, *Dept. of Physiology and Biochemistry, New York Medical College, Flower and Fifth Avenue Hospitals, New York.* The use of cation exchange resins for the group separation of the basic amino acids has been modified to permit the separation of histidine, arginine, and lysine from each other.

1 The protein is hydrolyzed with HCl and the excess acid is distilled.

2 The hydrolysate is passed over a column of cation exchange resin (Duolite C 1 or C-3, Amberlite IR-1, IR-100, XE-17, Ionac, etc., but not Zeo Karb) adjusted either to the hydrogen or to the ammonia cycle until the pH of the effluent is almost equal to that of the influent. This effluent, which is practically devoid of basic amino acids, is passed over a column of anion exchange resin, for the adsorption of the dicarboxylic amino acids.

3 The resin is washed with water.

4 Histidine and neutral amino acids are eluted with a weak base e.g. pyridine. The pyridine is removed by distillation. Histidine is readily isolated from the residue.

5 Arginine and lysine are removed from the column by ammonia. The ammonia is removed by distillation. The residue is taken up in dilute acid and the arginine is removed as the flavanate.

6 The filtrate and washings from 5 are passed over a cation exchange resin in the hydrogen phase. Flavaniac acid appears in the effluent from which it is recovered.

7 Lysine is removed from the resin either by exchange with the ammonia, or by elution with constant boiling HCl. The eluate is decolorized and the lysine hydrochloride is isolated.

Mechanism of *in vitro* and *in vivo* inhibition of cholinesterase activity by diisopropyl fluorophosphate. OSCAR BODANEK and ABRAHAM MAZUR, *Biochemistry Section, Medical Division, Chemical Warfare Service, Edgewood Arsenal, Md.* The inhibition of serum, red cell, muscle and brain cholinesterase activity of the rabbit, monkey and man by diisopropyl fluorophosphate (DFP) was studied. The negative log molar concentrations at which 50 per cent inhibition of the various cholinesterases occurred were as follows: 5.2 to 5.5 (red cell), 5.5 to 6.0 (brain), 5.4 (human

muscle), 4.1 (rabbit serum), 7.8 (monkey serum), 7.7 (human serum), 8.1 to 8.3 (horse serum). Rabbits and monkeys injected intravenously with DFP or exposed to DFP vapor showed decreases in cholinesterase activity of serum, brain and red cells which, in general, paralleled the *in vitro* sensitivities of these cholinesterases to inhibition by DFP. Men exposed to DFP vapor showed decreases in serum and red cell cholinesterases which also paralleled the *in vitro* sensitivities.

The inhibition of cholinesterase activity was irreversible as judged by failure of restoration of enzyme activity on dialysis or dilution of the DFP inhibited enzyme, and by the slow rate of regeneration of cholinesterase activity in animals exposed to or injected with DFP. For example, in the rabbit, about 5, 10 and 60 days were necessary for the restoration to normal of serum, red cell and brain cholinesterase activities, respectively.

The above results are discussed with regard to the questions of cholinesterase specificity and the appearance of cholinergic symptoms.

Methionine sulfoxide—a growth inhibiting analogue of glutamic acid. ERNEST BOREK (by invitation), PHYLLIS SHEINSS (by invitation) and HEINRICH WAELSCH, *Dept. of Biochemistry, New York State Psychiatric Inst. and Hospital, New York.* In an investigation of glutamic acid metabolism the effect of glutamic acid homologues, phenyl substituted derivatives and sulfur analogues were studied on the growth of *Lactobacillus arabinosus*—an organism for which glutamic acid is essential. Ethyl amino malonate, α amino adipic acid, or β phenyl glutamic acid (and its oxime) do not influence the growth of the organism.

Methionine sulfoxide inhibits growth completely. The inhibition is counteracted by L-(+)-glutamic acid, but not by aspartic acid or methionine. Data are presented on the effect of other homocysteine and cysteine derivatives on glutamic acid and aspartic acid metabolism.

Reinvestigation of the possible secretion of creatinine by the kidney tubules of the necturus. PHYLLIS A. BOTT, *Dept. of Physiological Chemistry, Woman's Medical College of Pennsylvania, Philadelphia.* In a series of experiments on *Necturus* anesthetized with urethane and injected with creatinine and inulin, the concentrations of these two substances were determined in serum and in glomerular fluid, tubular fluid or ureteral urine. For the determination of inulin in these experiments a new capillary method based on Harrison's modification of the Alving, Rubin and Miller method was used.

A new method for determining the site of collection of tubular fluid was devised. This consisted of the injection of neoprene into the tubule at the point of puncture with the formation of a cast by

treatment with acid After immersion in 1:1 hydrochloric acid for an hour the excised kidney was soft and the cast showing an extrusion of neoprene at the point of puncture was quickly separated from surrounding tissues

Tubular fluid/serum or urine/serum concentration ratios for creatinine and inulin agreed within the error of the entire experimental procedure (approximately 10 per cent) If the inulin concentration ratio is a measure of water reabsorption the results of these experiments indicate no secretion of creatinine by the kidney tubules of *Necturus*

Influence of iodination on tryptic activity
DONALD E BOWMAN *Dept of Biochemistry and Pharmacology, Indiana Univ School of Medicine, Indianapolis* Iodination of trypsin greatly reduces its blood pressure lowering properties and also diminishes its proteolytic activity Iodination may be carried out under conditions somewhat less drastic than the procedures frequently employed with various proteins At body temperature and at neutrality maintained by adequate buffer concentrations the reaction proceeds at a favorable rate The degree of iodination may be varied under these conditions by maintaining a slight excess of iodine for varying periods of time

The decidedly unfavorable influence of moderate decreases in either pH or temperature upon the rate of iodination of trypsin and other proteins also characterizes the iodination of histidine and especially tyrosine

Within limits the inactivation follows the degree of iodination However, present evidence indicates that it is possible to essentially eliminate blood pressure lowering properties with only a partial decrease in proteolytic activity Under given conditions proteolysis can be maintained by increasing the concentration of the iodinated enzyme while an increase in the amount of iodinated trypsin injected intravenously does not cause an appreciable fall in blood pressure

Under similar conditions partial iodination of the substrate also retards the proteolytic activity of untreated trypsin The digestion of casein or further loss of activity of an active protein such as insulin, through tryptic action, may be considerably retarded in this manner, the iodinated insulin itself retaining partial but significant activity

In view of the various correlations associated with trypsin-like enzymes and antitryptic factors, further study of the iodinated enzyme and its substrates is in progress

Folic acid in the prevention of abnormal feather pigmentation of chicks fed purified diets G M BRIGGS and R J LILLIE (Introduced by N R Ellis) *Univ of Maryland, College Park* Day-old New Hampshire chicks were fed a highly purified diet which contained the following ingredients

glucose, casein, gelatin, cystine, soybean oil, salts, thiamin, riboflavin, pantothenic acid, choline, nicotinic acid, pyridoxine, biotin, inositol, para-aminobenzoic acid, and the usual fat soluble vitamins At the end of the 4 weeks' feeding period, various deficiency symptoms were noted as reported previously, such as poor growth, retarded and rough feathering, anemia, perosis, and high mortality (Briggs, Luckey, Elvehjem, and Hart, *J Biol Chem*, 148: 163, 1943) When 4 weeks old, the surviving chicks were given a normal broiler ration which allowed body and feather growth to resume After 3 to 6 weeks on the broiler ration, a large percentage of the chicks developed wing and body feathers which contained large white areas and, often, abnormal black areas (as a result of the first 4 weeks' depletion period) Usually, only the tips of new feathers were abnormally pigmented, although well-formed feathers with none of the usual red pigment were quite common

Large numbers of chicks treated in an identical manner, but fed Wilson's Liver Fraction L (3 per cent) or synthetic folic acid (Lederle) for the first 4 weeks, developed normally in all respects including feather color throughout the entire growing period It was necessary to add at least 100 micrograms of folic acid per 100 grams of purified diet to prevent the abnormal feather pigmentation Higher levels of folic acid (200 micrograms per 100 grams of diet) were necessary to give growth equal to that obtained with Liver Fraction L

Analysis of basic organic compounds in biological tissues I Isolation prior to estimation
BERNARD B BRODIE, SIDNEY UDENFRIEND (by invitation) and JOHN E BAER (by invitation) *Goldwater Memorial Hospital and New York Univ, New York* A scheme for the analysis of basic organic compounds utilizing a number of simple general reactions has been useful in the development of analytical procedures for the estimation of antimalarials in biological fluids This provides for isolation of compounds from their metabolic products and from normally occurring substances by extraction procedures and the later application of a general but sensitive reaction to estimate concentration

Isolation and concentration are by extraction of free base into an organic solvent, and thence into an aqueous phase The organic solvent selected should exploit the finding that metabolic products of organic bases are commonly more water soluble than the parent substance Consequently the solvent of choice is one in which the compound is least soluble provided quantitative extraction is achieved A large fraction of the metabolic products may thus be left behind in the initial extraction, the remainder removed by suitable washes Extensive absorption of organic bases onto glass surfaces may be minimized with non-polar solvents

by the addition of alcohol subsequent to the initial extraction

A general technique to appraise specificity utilizes a comparison of solubility characteristics of a pure compound with those of apparent drug extracted from tissue. This examination yields information on solubility characteristics of interfering substances which may be used to modify the initial extraction procedure.

The final measurement is determined by the properties of the compound and involves fluorometry or microphotometry, directly, or after chemical alteration.

Analysis of basic organic compounds in biological tissues. 2. Estimation of fluorescent compounds. BERNARD B. BRODIE, SIDNEY UDENFRIEND (by invitation) and WESLEY DILL (by invitation). *Goldwater Memorial Hospital, and New York Univ., New York*. Sensitivity and simplicity of fluorometric assay make it the method of choice when possible. Fluorescence intensity depends upon environmental factors such as intensity of irradiation, solvent, temperature, pH, and the presence of quenching substances. These factors are controllable in an aqueous medium adjusted to the pH of maximal fluorescence intensity. The fluorescence properties of atabrine and other organic bases have been utilized in the design of extremely sensitive specific methods for their estimation in biological materials at concentrations as low as 5 micrograms per liter.

Atabrine is isolated from alkalinized plasma by extraction into ethylene dichloride. Drug metabolic products not separated in the initial extraction are selectively removed by washing the solvent with alkali. The drug is then returned to 0.1 N HCl and buffered to pH 9.5, where atabrine has its maximal fluorescence. Drug concentration is measured fluorometrically using appropriate standards. This procedure for human plasma is specific to the extent that it is subject to negligible interference from normally occurring substances or metabolic products of atabrine. Procedures for other fluorescent bases may differ in details because of differences in the solubility characteristics of the compound and/or its metabolic products and the pH required for maximal fluorescence.

Larger concentrations of many fluorescent organic bases analyzed directly in the organic phase after the addition of trichloroacetic acid. Speed and simplicity recommend this procedure when the concentration in the biological sample does not require excessive sensitivity on the part of the method.

Analysis of basic organic compounds in biological tissues. 3. Conversion to fluorescent compounds. BERNARD B. BRODIE, SIDNEY UDENFRIEND (by invitation), WESLEY DILL (by invitation), and THOROUGH CHENKIN (by invitation). *Goldwater*

Memorial Hospital and New York Univ., New York. Many non-fluorescent compounds yield fluorophores on treatment, the fluorescence of which may be used in the design of analytical procedures. Certain 4-aminoquinolines do so when subjected to ultraviolet irradiation under suitable conditions. The resulting fluorophores are oxidized, with loss of fluorescence, on further irradiation. This may be prevented and the fluorophore stabilized by the addition of cysteine. A variety of 4-aminoquinolines appears to yield the same fluorophore since there obtains the same relationship between molecular concentration and fluorescence intensity. These properties have been utilized in the design of specific methods for the estimation of SN-7618 (7-chloro-4-(1-methyl-4-diethylaminobutylamino)quinoline) and related compounds at concentrations as low as 10 micrograms per liter.

SN-7618 is isolated from alkalinized plasma by extraction into heptane. Ethyl alcohol is added to prevent adsorption onto glass surfaces. Drug metabolic products not separated are selectively removed from the solvent by alkaline wash. The drug is then returned to acid and buffered to pH 9.5, cysteine is added and the sample irradiated with a mercury vapor lamp. The concentration of fluorophore formed is measured fluorometrically using appropriate standards. The procedure for human plasma is specific to the extent that it is subject to negligible interference from normally occurring substances or drug metabolic products. The detail of procedures for other 4-aminoquinolines depends on the solubility characteristics of the compound and/or its metabolic products.

Other types of compounds have been analyzed by converting to fluorophores, e.g., SN-7744 (2-diethylaminomethyl-4-butyl-5-phenyl-1-phenol) by ultraviolet irradiation, and SN-S617 (2-methoxy-6-chloro-9-(4'-hydroxy-3'-diethylaminomethyl-phenylamino)acridine) by alkaline hydrolysis.

Analysis of basic organic compounds in biological tissues. 4. Coupling with diazonium salts. BERNARD B. BRODIE, SIDNEY UDENFRIEND (by invitation), and JOHN V. TAGGART (by invitation). *Goldwater Memorial Hospital and New York Univ., New York*. Many para-unsubstituted aromatic amines react readily with diazotized sulfanilic acid to form azo compounds which absorb light in the visible range of the spectrum. This reaction may be used in the design of analytical procedures. It is subject to negligible interference from organic extractable substances normally occurring in biological material. Consequently marked sensitivity may be achieved by coupling and making the final photometric measurement in a micro-volume. These properties have been utilized in the design of specific methods for the estimation of pamaquin and related 8-aminoquinolines in biological material at concentrations as low as 25 micrograms per liter.

Pamaquin is isolated from alkalinized plasma by extraction into petroleum ether. Isoamyl alcohol is added to prevent adsorption onto glass surfaces. No interfering metabolic derivatives of the drug are extracted. The drug is then concentrated by returning to a small volume of diazotized sulfanilic acid with which it couples. The resulting dye solution is assayed in a spectrophotometer or photoelectric colorimeter adapted to micro volumes. The overall procedure for other 8 aminoquinolines may vary in detail depending on the solubility characteristics of the compound and/or its metabolic products. The procedure for human plasma is specific to the extent that it is subject to negligible interference from normally occurring substances or drug metabolic products.

Aromatic amines possessing a free phenol group couple in neutral or slightly alkaline solution with p-nitroaniline-o sulfonic acid. This reaction has been used in analytical procedures for SN 6520 (1-naphthol-2-dimethylaminomethyl) and SN-5918 (4, 4'-dihydroxy-3, 3'-di(diethylaminomethyl)-diphenyl ether).

Analysis of basic organic compounds in biological tissues. 5. Salt formation with methyl orange. BERNARD B. BRODIE, SIDNEY UDENFRIEND (by invitation) and WESLEY DILL (by invitation), *Goldwater Memorial Hospital and New York Univ., New York*. Methyl orange salts of most organic bases are highly soluble in organic solvents. The base may, therefore, be assayed indirectly through the extraction of its methyl orange salt into an organic phase and the measurement of the concentration of methyl orange achieved. This is a general reaction and has been used in the design of analytical procedures for a number of organic bases not otherwise analysable. The procedure as first reported used ethylene dichloride as the solvent. The sensitivity of the reaction in this solvent is limited by the slight solubility of free methyl orange in ethylene dichloride and the reaction of this dye with normally occurring organic bases extractable from the biological material. The use of the less polar solvent, benzene, minimizes these difficulties since neither methyl orange nor the normally occurring biological substances which interfere are soluble in this solvent to an appreciable extent. Consequently an increase in sensitivity (about tenfold) may be achieved by returning the methyl orange from the benzene to a small volume of acid, and assaying its concentration by microphotometry. This permits the estimation of cinchonine and other benzene soluble organic bases in plasma at concentrations in the order of 50 micrograms per liter.

Cinchonine is isolated from alkalinized plasma by extraction into benzene. Its metabolic products are left behind. Isoamyl alcohol is added to prevent adsorption onto glass surfaces. The benzene phase is

shaken with methyl orange solution. The methyl orange which dissolves in the solvent through salt formation with the organic base is returned to a small volume of acid and measured photometrically. Standards must be run concurrently in the procedure.

Intermediates of acetoacetate oxidation. JOHN M. BUCHANAN (by invitation), WARWICK SAKAMI (by invitation), SAMUEL GURIN and D. WRIGHT WILSON, *Dept. of Physiological Chemistry, Univ. of Pennsylvania, Philadelphia*. Extracts of rabbit kidney were prepared by adding 10 cc. of 2 M sodium phosphate buffer (pH, 7.6) containing magnesium ions to 10 gms. of rabbit kidney, homogenizing in a Potter-Elvehjem apparatus and centrifuging the resulting suspension for 15 minutes at 3000 R.P.M. The supernatant was cell-free but contained cellular debris. Acetoacetate is oxidized readily by this preparation provided α -ketoglutarate is added. Citric acid when added alone is likewise readily metabolized. Thus, this extract differs from the preparation of Hunter and Leloir, which forms citric acid from acetoacetate and oxalacetate but which does not oxidize citric acid. Acetate (and acetyl phosphate in the presence of sodium fluoride) are not metabolized to an appreciable extent.

Possible two-carbon intermediates of acetoacetate oxidation in this extract are being studied with C^{13} . Isotopic acetoacetate together with non-isotopic acetate and α -ketoglutarate was added to the extract, which was incubated aerobically at 38° for 40 minutes. At the conclusion of the experiment, acetic and α -ketoglutaric acids were isolated. The ketoglutarate was oxidized to succinate. It was found that the C^{14} concentration of the succinate was about three times that of the acetate.

If acetate were an intermediate in the conversion of acetoacetate to α -ketoglutarate, the C^{13} concentration of the acetate should have been greater than that of the α -ketoglutarate. Therefore these experiments indicate that acetate is not a direct intermediate of acetoacetate oxidation in this extract although some is formed from acetoacetate. Similar experiments are underway with acetyl phosphate.

Cobalt inhibition of tissue respiration, glycolysis, and growth. DEAN BURK and (by invitation) ARTHUR L. SCHADE, MARIE L. HESSELBACH, and CLARA E. FISCHER, *National Inst. of Health, Bethesda, Maryland and Overly Biochemical Research Foundation, New York*. Cobalt is an effective inhibitor of growth of certain aerobic and anaerobic microorganisms, and the inhibition may be overcome by histidine. Respiration is also inhibited by Co, but secondarily.

Cobalt inhibited the respiration of mouse tissue slices suspended in glucose Ringer-phosphate medium as an increasing function of 1) concentration of Co (over the approximate range 5 to 50 p.p.m.,

added as e g CoCl_2 , 2) time (progressive for several hours), and 3) organ, in the approximate order brain, liver, placenta, skeletal muscle, spleen, kidney, heart, lung, tumor (spontaneous breast carcinoma) and embryo. With the tumor tissue, 10 p p m Co gave somewhat over 50 per cent inhibition by three hours. Complete inhibition was never obtained with any Co concentration, exposure time, or tissue tested. The tissue slice respiration of tumors taken from mice previously injected with Co was markedly below normal.

Anaerobic and aerobic glycolysis of the carcinoma slices suspended in glucose Ringer bicarbonate medium was affected little if at all at Co concentrations one to two orders higher than those inhibiting respiration. Co raised the R Q 0.1 to 0.2, to just above 0.90.

The logarithmic velocity constant of growth of breast tumors in C3H mice receiving injections of approximately 0.1 mg of Co daily was 25 per cent less than in untreated controls ($P = 0.01$), intratumoral injections being somewhat more effective than more remote modes of injection tested. Tolerance doses of Co for mice could be raised many fold by concurrent injections of histidine, at dosages little greater than molecularly equivalent.

Effect of solvent upon utilization of beta-carotene for vitamin A storage. ELIZABETH C CALLISON (by invitation) and ELSA ORENT-KEILES, *Bureau of Human Nutrition and Home Economics, U S D A, Beltsville, Md.* Six groups of rats consisting of four males and four females each, averaging 21 to 29 days of age and 46 to 56 gms in weight, and possessing small initial stores of vitamin A, were placed on a vitamin A-free diet, consisting of 18 per cent extracted casein, 15 per cent dried yeast, 4 per cent Osborne and Mendel Salt Mixture, 10 per cent hydrogenated cottonseed oil, 53 per cent cornstarch, and viosterol.

Crystalline beta carotene in three different media was fed thrice weekly at two levels, 72 and 144 mcg respectively, per kilogram body weight per day. Solutions of carotene in ethyl laurate, peanut oil, and cottonseed oil, respectively, with added hydroquinone were prepared at weekly intervals and stored at 0°C between feedings. No deterioration was detected at any time during the study as determined by periodic examination by means of the Coleman, 10 S, spectrophotometer.

There were no significant differences in growth rate at each carotene level among the three groups of animals. At 90 days of age the animals were killed and the livers analyzed for vitamin A by means of the antimony trichloride reagent, using the Evelyn photoelectric colorimeter. Although the basal diet diet itself contained 10 per cent fat (hydrogenated cottonseed oil), marked differences in liver stores of vitamin A were found, depending upon the lipid in which the carotene was fed. Ethyl laurate pro-

moted practically no storage of the vitamin, peanut oil was somewhat more efficient, while cottonseed oil was definitely superior to the other two.

Thymus nucleate and the heat coagulation of aqueous tissue extracts. CHARLES E CARTER (by invitation) and JESSE P GREENSTEIN, *National Inst of Health, Bethesda, Md.* Fresh aqueous extracts of rat liver and spleen are not coagulable upon heating at 98°C for several hours. Incubation of such extracts for 4-5 hours destroys the natural protection against heat coagulation without an appreciable change in pH. The addition of thymus nucleate restores the protection although enzymatic activity is lost from such mixtures. Mixtures of aqueous extract of liver and added thymus nucleate when incubated likewise become progressively susceptible to heat coagulation. Aqueous extracts of rat muscle coagulate almost immediately upon heating but can be protected against coagulation by addition of thymus nucleate. One c cm of aqueous liver extract equivalent to 166 mg of tissue which had been previously incubated could be protected against heat coagulation at 98°C for over 3 hours by 0.6 mg of thymus nucleate in a total volume of 2 c cm. Below this concentration thymus nucleate conferred little or no protection. Addition of small amounts of metallic ions destroyed the thymus nucleate protection against heat coagulation. Mixtures of liver extract and thymus nucleate which were not coagulated on heating at 98°C for 1 hour and which were subsequently cooled, coagulated after 15-30 minutes incubation with desoxyribonuclease activated with Mg^{++} . Desoxyribonuclease or magnesium ion alone under these conditions did not produce coagulation. Thymus nucleate depolymerized by irradiation gave results identical with those obtained in experiments using highly viscous solutions of nucleate, yeast nucleate conferred no protection against heat coagulation upon aqueous tissue extracts.

Thymus nucleate and the heat coagulation of egg albumin. CHARLES E CARTER (by invitation) and JESSE P GREENSTEIN, *National Inst of Health, Bethesda, Md.* Aqueous, salt free solutions of crystalline egg albumin at pH 6.9 immersed in boiling water yield almost immediately a dense turbidity. Clear mixtures of egg albumin and dialyzed sodium thymus nucleate (Hammarsten) at pH 6.9 and at a ratio of close to 1 mg of nucleate to 600 mg albumin, when similarly heated at 98°C, remain clear for at least six hours at this temperature. The minimum protective proportion of nucleate is sharply defined, for albumin solutions containing a slightly lower proportion of nucleate than the above are almost immediately heat coagulable. Any higher proportion of nucleate confers an almost indefinite protection against heat coagulation of the protein. The minimum protective ratio of 1 mg nucleate to 600 mg albumin is inde-

pendent of the presence of NaCl up to 0.2 per cent. At higher concentrations of NaCl, heat coagulation of the albumin occurs no matter how much nucleate is present. Identical results are obtained with thymus nucleate depolymerized by irradiation with ultraviolet light. The number of $-SH$ groups liberated by heat is the same in the presence as in the absence of nucleate, and is only a small proportion of the amount liberated by guanidine HCl. Yeast nucleate and agar are ineffective in protecting egg albumin against heat coagulation. When NaCl is added to a mixture of albumin and nucleate which had been heated and cooled no coagulation results. Such coagulation occurs only when salt is added prior to heating.

An unidentified factor essential for rat growth. C. A. CARY and (by invitation) A. M. GARTMAN, L. P. DRYDEN, and G. D. LIKLY. *Bureau of Dairy Industry, Agricultural Research Administration, Washington, D. C.* Rats at weaning ordinarily contain a still unidentified factor (X) which affects their growth and development on a diet (A) adequate in all known nutrients. Young may be depleted of X by feeding their mothers a diet deficient in X. Casein prepared by centrifugation from milk was a good source of X; commercial, Sherman vitamin A-free, SMA and Labco caseins contained different amounts of X, but, when 20% or 40% of casein (C), prepared by 10 six-hour extractions with hot alcohol, was fed in diet A (containing 5% of yeast protein) to X-deficient rats, growths were 54% and 25% of normal respectively, coagulated egg albumin gave growths similar to casein C, and with 60% of casein C the rats generally died within 2 weeks. On diet A with 25% of lactose and 20% of casein C growth was 36% of normal. When a few milligrams daily of certain commercial liver extracts were fed separately from diet A to sex-litter mates of the above rats, growth was normal or approximately normal except with 60% casein (85% normal). A few micrograms of a crude concentrate of X fed separately, gave normal growth when tested with the 20% casein diet. Increments in "growth" involved the fat-free dry weight, and were due principally to increased feed consumptions. X from liver extracts is water-soluble, dialyzable and precipitable with ammonium sulphate.

Relation between urinary excretion of thiamine and pyrimin (the pyrimidine-like component of thiamine). W. O. CASTER (by invitation), OLAF MICKELSEN and ANCEL KEYS. *Lab. of Physiological Hygiene, Univ. of Minnesota, Minneapolis.* Young men were maintained for periods of two to seven months on known thiamine intakes ranging from 0.5 to 10 mg per day. Thiamine and pyrimin excretions stabilized only after a period of about six weeks following changes in thiamine intake. The thiamine excretions are characteristic of the

individuals as well as of the intake. In two groups of six subjects maintained on 1.0 and 2.0 mg of thiamine per day, the correlation between the levels of thiamine excretion of the individual subjects for two three-day periods, seven months apart, was 0.91 for the entire group. When the thiamine intakes for two groups were reversed, the correlations between the thiamine excretion of each subject during the two periods was 0.89 and 0.94 for each of the two groups. In general, the thiamine excretion shows a substantially linear relation to the intake, whereas the pyrimin excretion similarly rises with increasing thiamine intake but tends to plateau at about 0.40 mg excretion per day. The pyrimin excretion for thiamine intakes of 0.6 and 2.0 mg per day averaged 0.138 and 0.231 mg per day, respectively, with intra-individual variations of 0.025 to 0.029 mg, and inter-individual variations of 0.018 to 0.024 mg in different groups. The parallel thiamine excretions were 0.005 to 0.224 mg per day with intra-individual variations, respectively, of 0.006 and 0.031 and inter-individual variations of 0.006 and 0.106 mg. For each level of thiamine intake, the excretion of thiamine is much more variable on a percentage basis than is pyrimin excretion.

Effect on adrenal constituents of injury to the rat. ALFRED CHANUTIN and STEPHAN LUDEWIG. *Biochemical Lab., Univ. of Virginia.* The water, nitrogen, total lipid, cholesterol (free and total) and phospholipid contents (mg/100 gm body weight) of the adrenals of rats were determined after injecting mustard (dichloroethyl sulfide) and 3 nitrogen mustards (ethyl-bis (chloroethyl) amine, methyl-bis (chloroethyl) amine, tris (chloroethyl) amine). The water, protein and phospholipid contents of the adrenals increased while the total lipids and cholesterol contents decreased after injection. Adrenal hypertrophy was noted in all cases. The increase in water content was chiefly responsible in accounting for the increased adrenal weights.

The percentage concentration of adrenal nitrogen and phospholipid remained constant. There were slight increases in the per cent of water and appreciable decreases in the concentration of the total lipids and cholesterol. The data were converted to mg/100 gm body weight so that adrenal weight and body weight could be considered.

A striking increase in the per cent of the free cholesterol was noted in many cases, particularly when the total cholesterol was markedly diminished.

In order to assess the effect of another type of injury on the cholesterol content of the adrenals, anesthetized rats were scalded by dipping the clipped backs in water at 75°C for 60 seconds. The total cholesterol decreased markedly and the per cent of free cholesterol increased. Nembutal anes-

thesia alone caused a decrease in cholesterol content. It may be concluded that noxious stimuli have a marked effect on the cholesterol metabolism of the adrenals.

A nucleoprotein from avian tubercle bacilli
ERWIN CHARGAFF *Dept of Biochemistry, Columbia Univ., New York*. Borate buffer (pH 8.2 to 8.5) extracts of avian tubercle bacilli (grown on Sauton medium) yield, on centrifugation at high speed (31,000 grams), a fraction of bacterial glycogen of very high particle weight (E. Chargaff and D. H. Moore, *J. Biol. Chem.*, 155: 493, 1944). The supernatant contains, in addition to small amounts of glycogen, a nucleoprotein giving strong color reactions for desoxy-pentose nucleic acid and exhibiting an absorption maximum in the ultra violet at 2590 Å.

Although the nucleoprotein solutions thus obtained are, in most cases, homogeneous electrophoretically, the isolated protein preparations (containing 9 to 10 per cent N, 0.7 to 0.9 per cent P) can be fractionated further when use is made of the fact that the nucleoprotein is insoluble at pH 4.3, but soluble at half-saturation with ammonium sulfate. In this manner, preparations containing as much as 3.2 per cent P (N 12.1 per cent) may be obtained.

The protein moiety of the nucleoprotein does not appear to be a histone or protamine. The nucleic acid, whose isolation has been effected by a variety of means is, in the main, of the desoxy-pentose type, small amounts of pentose nucleic acid are also present. In this connection, a method for the purification of highly polymerized desoxyribose nucleic acid has been developed which is based on the conversion of lanthanum nucleate to the potassium salt by treatment with 1 M potassium chloride (containing 5 per cent of potassium oxalate).

Comparison of the Absorption of Ester and alcohol vitamin A by human subjects
S. W. CLAUSEN, A. B. McCOORD (by invitation) and B. L. GOFF (by invitation) *Dept of Pediatrics, Univ. of Rochester School of Medicine*. Patients suffering from celiac disease, cystic fibrosis of the pancreas, intestinal tuberculosis, catarrhal jaundice and giardiasis absorb ester vitamin A poorly after oral administration. Two factors found to be necessary for the absorption of vitamin A are the presence of bile salts in the intestinal tract and normal intestinal motility. The present communication shows that a third factor, present in pancreatic secretion, is necessary for the absorption of vitamin A ester.

Most children with cystic fibrosis of the pancreas, who are deficient in pancreatic enzymes, absorb ester vitamin A normally when it is given orally with Pancreatin, a preparation which contains the pancreatic enzymes. Children with celiac disease, the cause of whose inability to absorb vita-

min A is not known, do not absorb ester vitamin A in the presence of Pancreatin.

When alcohol vitamin A was given orally, 2 children with cystic fibrosis of the pancreas showed excellent absorption, but a child suffering from celiac disease showed poor absorption. Two children suffering from chronic malnutrition absorbed alcohol much better than ester vitamin A.

While more observations are needed, our studies suggest that assimilation of vitamin A ester involves saponification in the duodenum, absorption of vitamin A alcohol in the upper small intestine, and reconversion of the alcohol to an ester before it reaches the circulation. The observation that absorbed vitamin A in the blood, even in cases of cystic fibrosis of the pancreas, appears as the ester indicates that the enzyme that causes the esterification is not pancreatic lipase.

Role of amides in urea synthesis
PHILIP P. COHEN and MIKA HAYANO (by invitation) *Dept of Physiological Chemistry, Univ. of Wisconsin, Madison*. The role of amides and the corresponding ammonium salts in urea synthesis by rat liver slices was investigated. It was found that with starved slices the rate of synthesis from glutamine and ammonium glutamate was equal, but greater than that from ammonium-chloride. With well fed slices, the rate of urea formation from ammonium-glutamate was greater than that from ammonium-chloride which in turn was greater than that from glutamine. The addition of ornithine or citrulline to starved slices increased the rate of urea formation from ammonium glutamate to a value twice that from glutamine and three times that from ammonium chloride. These findings suggest that in starved slices the concentration of ornithine or citrulline may be a limiting factor. With starved slices the rate of urea synthesis from asparagine, lactamide and succinamic acid was greater than that from ammonium chloride but less in the case of well fed slices. The corresponding ammonium salts did not show the marked increase in rate of urea synthesis observed with ammonium glutamate, the rates of the former remaining between those of ammonium-chloride and the corresponding amides in both starved and well fed tissue. Of a series of aliphatic and aromatic amides tested the above four alone were active in urea synthesis. It would appear from these findings that glutamine and related amides do not play a specific role in the urea cycle. However, the consistent accelerating effect of ammonium glutamate over other ammonium salts, suggests that glutamate may play some specific role.

The constitution of that rickettsial and soluble rickettsial antigen derived from the epidemic typhus vaccine
By SEYMOUR S. COHEN (introduced by W. M. Stanley) *Children's Hospital and the Univ. of Pennsylvania*. Rickettsia prowazekii

and the soluble antigen (S) were isolated from phenol-treated typhus vaccines by low and high speed centrifugation, respectively. The rickettsiae were disrupted by sonic vibration and fractionated into a low speed sedimentable fraction, a high speed sedimentable fraction, and a high speed non-sedimentable fraction. S was similar only to the rickettsial high speed sedimentable fraction, after digestion by proteolytic enzymes. A protease of the yolk sac endothelium degraded rickettsiae. S is probably a proteolytic degradation product of rickettsial substance arising at some stage of the host-virus interaction.

Rickettsial antigens did not crossreact significantly with antisera to the host antigens.

The sedimentable fractions of rickettsiae are particulate aggregates comprising 90-95 per cent of the virus. The non-sedimentable fraction contains no dialysable material and contains all the nucleic acid of the virus. This comprised 2-2.5 per cent desoxyribose nucleic acid which was isolated and characterized. This substance was not soluble before vibration. There is no evidence that any material of a particle weight of less than millions existed within rickettsiae.

The lipid, carbohydrate, tyrosine, tryptophane, and arginine contents of rickettsial fractions were determined.

The reducing sugar of the antigens before acid hydrolysis was equivalent to the total carbohydrate of the fractions, which gave aldehyde reactions. Aldehyde reagents, such as phenyl hydrazine-p-sulfonic acid and sodium sulfite were successfully used in the specific precipitation of S on a large scale.

Enzymatic formation of guanine by a reversible phosphorolytic cleavage of ribonucleic acid. SIDNEY P. COLOWICK and WINSTON H. PRICE (by invitation) *Dept. of Pharmacology, Washington Univ., School of Medicine, St. Louis*. Aqueous extracts of rat muscle contain an enzyme which catalyzes a reaction between ribonucleic acid and inorganic phosphate, the products being free guanine and a derivative of ribonucleic acid in which the guanine groups have been replaced by phosphate groups.

This derivative ("P-ribonucleic acid"), which can be isolated by precipitation with a basic protein (salmine) at pH 6, contains acid-labile P equivalent in amount to the free guanine liberated in its formation. The acid-labile P is split off almost completely in 1 minute in 0.33 N HCl at 30°. For each mole of inorganic P liberated by acid hydrolysis, reducing power equivalent to that of 1 mole of ribose appears.

These findings indicate that P-ribonucleic acid contains ribose-1-phosphate linkages, formed by the reaction of phosphate with the ribose-1-guanine linkages of ribonucleic acid. The enzyme catalyzing

the reaction may therefore be called "ribonucleic acid phosphorylase" in analogy with the polysaccharide, disaccharide, and nucleoside phosphorylases already known.

The new reaction, like other reactions of the phosphorylase type, is measurably reversible. P-ribonucleic acid reacting with guanine to form ribonucleic acid and inorganic phosphate. The equilibrium constant,

$$\frac{[\text{-ribose 1-phosphate linkages}] \times [\text{guanine}]}{[\text{-ribose-1-guanine linkages}] \times [\text{phosphate}]}$$

is approximately 0.02 at 30°, pH 7.5.

The enzyme is specific for ribonucleic acid. Other compounds containing the ribose-1-guanine linkage (desoxyribonucleic acid, guanosine, guanylic acid) are not attacked. Arsenate cannot serve in place of phosphate for the reaction with ribonucleic acid. The enzyme is completely inactivated by 0.002 M iodoacetate in 30 minutes at 30° and pH 7.5.

A tracer study of iron metabolism with radioactive iron absorption, excretion, utilization and storage. D. HAROLD COPP (by invitation) and DAVID M. GREENBERG, *Univ. of California Medical School, Berkeley*. This work was intended to be presented a year ago and an abstract was published in the *Federation Proceedings* 4: 86, 87 (1945). The work has not been published in detail to date.

Method for the determination of mannitol in blood and urine. A. C. CORCORAN and IRVINE H. PAGE (with the assistance of R. H. HARRIS) *Cleveland Clinic Foundation, Cleveland*. The use of mannitol clearance as a measure of glomerular filtration rate led to the search for a method of its determination which would be simpler than those presently available.

The method follows a sample of diluted urine or plasma filtrate (Somogyi 1/15) in a test tube at 25°C is brought to concentrations of 0.0013 M KIO_4 and 0.1 N H_2SO_4 . The oxidation is allowed to proceed for 10 minutes, at which time it is interrupted by addition of 36.6 mM SnCl_2 per liter of reacting mixture. At this stage, the oxidation of mannitol is complete, yielding approximately 2 M formaldehyde per 1 M mannitol, while no formaldehyde has yet been formed from glucose. The formaldehyde concentration of the mixture is then determined by the method of MacFadyen (*J. Biol. Chem.*, 158: 107, 1945) using the Coleman Model 6 spectrophotometer.

The "blank" in fresh dog plasma averages 7.6 mg per 100 cc, expressed as mannitol and may be attributed in part to ascorbic acid. The substances responsible for the "blank" disappear from plasma on long standing. Treatment of plasma or plasma filtrate with washed yeast results in the formation of a substance, possibly di-phosphoglyceric acid which is oxidized to yield formaldehyde.

The advantages of the method lie (1) in the elimi-

mation of the need for yeast-treatment of blood or urine and (2) in the rapidity and ease of the colorimetric procedure. The observed equality of simultaneous diastase, mannitol and creatinine clearances in dogs testifies to the accuracy of the procedure.

Influence of insulin on consumption of oxygen by slices of liver in the presence of succinate and related substrates. **ELMER C. CONLEY** and **FRANK D. SCHMIDT** (by invitation). *Penn. University, Lafayette, Indiana*. The results reported have been obtained with liver slices, about 0.5 mm. in thickness, suspended in isotonic phosphate buffer solution (pH = 7.4; NaCl = 64.6% in Waring blenders). The substrates studied have been added to give 0.01 M concentration.

In confirmation and extension of the observations previously reported (Federation Proceedings 1944) it has been found that in the presence of succinate, pyruvate or citrate respectively, but not in the presence of fumarate, malate or α -ketoglutarate, the addition of insulin was followed by an increase in the consumption of oxygen by liver slices from fasted white rats.

The addition of insulin was followed by an increase in the consumption of oxygen by sliced liver tissue from rats made diabetic by the intramuscular injection of alloxan, in the presence of fumarate, malate or α -ketoglutarate respectively, as well as in the presence of succinate, pyruvate, or citrate respectively, although the increases with each of the latter three substrates were possibly significantly less than the increases in the presence of insulin with liver slices from healthy fasted rats.

Metabolic products of several synthetic antimalarials in the human. **LESLAY C. CRAIG**, and (by invitation), **ELYCE T. TUCKER**, **HAROLD MIGNON**, **CALVIN GILLESPIE** and **MALCOLM SIEGEL**. *Eckstein Inst. for Medical Research, New York*. An attempt has been made to isolate from the urine of patients receiving an antimalarial, possible transformation products of the drug and in this way obtain information regarding its fate in the body. Four different synthetic antimalarials as listed were chosen for the investigation:

773 (7-chloro-4-(4-diethylamino-1-methyl-1-butylamino)quinoline)

5584 (1-(7-chloro-4-quinolylamino)-3-diethylaminopropene)

5137 (1-(7-chloro-4-quinolylamino)-3-diethylamino-2-propanol)

1771 (4-(7-chloro-4-quinolylamino)-2-diethylaminomethylphenol)

The collected urines were successively extracted by different solvents and the material in the extract investigated by various fractionation procedures mainly involving the "Counter-Current" distribution method. This has resulted in the isolation of a transformation product from each of the four drugs

which has given analytical data in good agreement for a substance with a $C_{10}H_{11}$ removed. De-ethylation is thus suggested and has been confirmed in the case of 5584 and 7613 by comparison with synthetic material. The two latter substances are themselves highly active against bird malaria. The de-ethylated 7613 from urine is optically active $[\alpha]_D^{25} = -145^\circ$, as was also the 7613 drug recovered. Contrasted to this result was that obtained with 5137 even though the latter contains an asymmetric carbon atom.

A further transformation product from each of the drugs except 7613 has been isolated and characterized. Analytical data suggest possible structures but the exact identity at present is not certain. Absorption spectrum studies indicate the quinoline nucleus to be involved only in the case of 1771.

Metabolism of excess nicotinamide by the chicken. **W. J. DANN** and **JESSE W. HURY** (by invitation). *Depts. of Physiology and Biochemistry, Duke Univ. School of Medicine, Durham*. When chicks are given a complete mash feed to which 2 per cent of nicotinamide is added, they excrete large amounts of "nicotinic acid", as estimated by the König reaction applied to aqueous extracts of the droppings. Unless the specimens are dried or autoclaved after collection, rapid loss of the nicotinic acid may occur. The apparent nicotinic acid content is greater after alkaline hydrolysis of the droppings than before, suggesting the presence of a nicotinic acid precursor presumably in combination with other molecules.

Both a hot methanol extract of the dried droppings and a hot aqueous extract of moist droppings concentrated by adsorption of the nicotinic acid on Lloyd's Reagent with subsequent elution yielded solutions which contained both free and combined nicotinic acid. Continuous extraction of aqueous solutions at pH 2.0 with ether served to remove the free nicotinic acid. The residual solution of combined nicotinic acid was evaporated to dryness and the ground residue extracted with boiling methanol.

Attempts to isolate the nicotinic acid containing compound led to the separation of a crystalline picriclone. Decomposition of the picriclone and hydrolysis of the product without isolation was followed by the isolation of pure nicotinic acid and also orlistine from the solution. It thus appears that the chicken disposes of excess nicotinamide in a manner similar to that in which it handles benzoic acid.

Regulation of phosphorylations in anaerobic glycolysis of red cells by its intermediary products. **ZACHARAS DISCHER**. *College of Physicians and Surgeons, Columbia University, New York*. In hemolysates of human red cells containing M/40 mg M 50 NaF and M/20 sodium bromacetate

ATP transphosphorylates with glucose under formation of Harden-Young Ester and triosephosphate. This reaction is strongly inhibited by 1-phosphoglyceric acid at M/300 and completely by phosphopyruvic acid at M/1000. 2,3-Diphosphoglyceric acid inhibits only slightly at M¹/50 and α - and β glycerophosphates are without influence. When Harden-Young Ester and pyruvate are added to a hemolysate containing M/50 NaF, triosephosphate is formed and is oxidized while pyruvic acid is reduced. This process is coupled with phosphorylation of ADP and adenylic acid. The coupled phosphorylation is inhibited by monophosphoglycerate at M/300 and phosphopyruvate at M/1000.

When citrated human blood is kept for 24 hours at 4° H-Y Ester and triosephosphate accumulate in the erythrocytes. These esters remain in cells when these are washed with saline. When washed erythrocytes loaded with H-Y ester are kept for 30' at 40° the ester breaks down to lactic acid. M/100 sodium bromoacetate immediately stops this breakdown. Oxidation of triosephosphate should be accompanied by an esterification of inorganic P. Comparison of the content of inorganic P in samples with and without bromoacetate shows, however, that no visible esterification of P occurs during the breakdown of the H-Y ester. If, however, pyruvate in excess is added the breakdown of the H-Y ester is coupled with esterification of inorganic P though the total turnover is only slightly increased by pyruvate. Possible mechanisms of these effects on phosphorylation are discussed.

Characteristic and sensitive color reaction of SH-compounds ZACHARIAS DISCHE *College of Physicians and Surgeons, Columbia Univ* Skatole, indole 3-acetic, -propionic and -butyric acids, tryptophane and tryptamine give a brown color with derivatives of furfural formed from sugars by H₂SO₄ above 70°. When SH-compounds (cysteine, glutathione, thioglycolic acid) are present in the solution a pink color appears. This reaction can be used to detect SH-compounds in the presence of an excess of the indole derivatives or to detect these derivatives in the presence of an excess of SH-compounds. Under certain conditions, methionine reacts in the same way apparently after being split to homocysteine. For quantitative determinations the following procedure proved satisfactory. Mix 1 part 0.01% solution of glucose with 6 parts H₂SO₄ (analyt. reagent). Let stand until cool. 4 cc. of the mixture are added with ice cooling to 1.65 cc. of a solution containing 5-20 γ /cc. cysteine. After 3 minutes, 0.15 cc. of 0.12% solution of tryptophane is added. A blank with water is prepared. A pink color develops. The intensity is measured after 5 hours in a photoelectric colorimeter with filter 52. Cystine is determined after reduction by NaCN (analyt. reagent). Glutathione gives a color

60% stronger than corresponds to its cysteine content. It can be determined in 0.1 cc. of blood deproteinized with metaphosphoric acid. Amino acids present in proteins, do not interfere in 0.2% solution, except methionine, which gives an absorption corresponding to 1% of its weight of cysteine, but with a different absorption spectrum. When the mixture of the solution and H₂SO₄ is heated for 20' at 100° before the addition of tryptophane, methionine can be determined in solutions containing 10 γ /cc.

Maintenance of active hemoglobin—a function of erythrocytes DAVID L. DRABKIN *Dept. of Physiological Chemistry, School of Medicine, Univ. of Pennsylvania* The phenomenon of reductive reversion of ferrihemoglobin (methemoglobin, MHB, inactive in the oxygenation equilibrium) to active ferrohemoglobin, Hb, in drawn blood on standing appears to be an expression of an important physiological process, intimately bound up with glycolytic reactions in the erythrocyte.

The simultaneous increase in active hemoglobin (measured spectrophotometrically by determination of the equilibrium ratio of HbO₂ to HbO + MHb) and disappearance of glucose (decrease in reducing values upon Somogyi filtrates) were systematically investigated, particularly from the standpoint of the agents which inhibit the reversion of MHb, and the factors which can overcome this inhibition. Freshly washed erythrocytes, mainly of the dog, were used. The HbO₂ was partially converted intracellularly (to the extent of 50 per cent) to MHb by means of 0.15 M KNO₂ (0.25 mole KNO₂ per 1.0 mole HbO₂ being employed). Concentrated suspensions of the MHb-HbO₂ erythrocytes were made up in an approximately isotonic medium containing glucose and phosphate buffer, and the suspensions were incubated aerobically in a water thermostat at 38°C. Aliquots for analysis were removed periodically during 2 to 3 hours of incubation. The following results were obtained. Reversion of MHb and glycolysis were inhibited by (a) hemolysis, (b) addition of fluoride, and (c) addition of iodoacetate. The inhibition with fluoride was overcome regularly by means of addition of pyruvate, but not by lactate. The iodoacetate inhibition could not be removed.

The experiments implicate both the coenzyme I down and II systems in the reversion of MHb.

Effect of morphine on the oxygen saturation of arterial blood ANNA J. EISENMAN *Research Dept., U. S. Public Health Service Hospital, Lexington, Ky.* Twelve experiments were done on ten subjects, all former morphine addicts. Blood was collected from the femoral artery and defibrinated anaerobically and analyzed for oxygen content and capacity and in most cases for serum carbon dioxide content by means of the Van Slyke manometric

apparatus Large single doses of morphine sulfate (75 to 175 mg) were administered Blood was again collected at the peak of the subject's reaction, as manifested by mild narcosis, the head falling forward on the chest, talkativeness or drowsiness This state was usually attained in about three hours after the administration of the drug In all twelve cases, the oxygen saturation of the blood decreased from two to eighteen per cent The oxygen capacity did not vary much from the original value, the maximum change, an increase of one volume per cent, was noted in the case of a patient who had vomited In eight of ten cases the serum carbon dioxide content increased about three volumes per cent This increase was not proportional to the drop in oxygen saturation The variations were unrelated to the amounts of morphine administered but showed rough relationship to the subject's reaction as objectively observed One individual who reacted only mildly to the maximum dose of 175 mg sustained minimal blood changes The striking observation from these studies is the small magnitude of the changes resulting from relatively large doses of morphine These changes in the blood can be demonstrated only at the time of maximum reaction

Phosphate exchange in bone using radiophosphorus in vitro MARLENE FALKENHEIM (by invitation) and HAROLD C HODGE *School of Medicine and Dentistry, Univ of Rochester, Rochester* *In vitro* experiments in which powdered bone ash was exposed to solutions of Na_2HPO_4 containing P_{32} have shown that bone adsorbs P_{32} The mechanism was unknown

Radioactivity determinations have been supplemented by chemical analyses of the bone and solutions Although the P_{32} concentration rises in the bone with increasing time of exposure, no large order transfers of phosphate occurred either from the solution to the bone or in the opposite direction Description was found to be as rapid and as complete as adsorption The mechanism can be adequately accounted for by an exchange reaction

The exchange, which initially is quite rapid, seems to approach a maximum in 7 days, although at that time not all the phosphate has exchanged In fact, 19% of the total bone phosphate seems to represent the exchangeable portion

Preparation of dried hemoglobin without loss of activity LEE E FARR and ALMA HILLER *Hospital of the Rockefeller Inst for Medical Research, New York* The purpose of the work was to attempt to prepare, as a blood substitute, hemoglobin in an active, easily portable form Applying to oxygenated hemoglobin solutions the technique for freezing, drying and preserving *in vacuo* in common use for plasma gave preparations in which the hemoglobin had lost 25 to 30 per cent of its oxygen binding capacity, by change to methemoglobin

However, when hemoglobin solutions were first deoxygenated by repeated evacuation of all gases, so that over 99 per cent of the oxyhemoglobin was changed to reduced hemoglobin, the reduced solutions could then be frozen and dried in ampoules and the dried hemoglobin kept *in vacuo* for months without methemoglobin formation In redissolving the reduced hemoglobin, it was necessary to prevent even momentary access of atmospheric oxygen to the dried material before it was dissolved, or met-hemoglobin was formed After the reduced hemoglobin was in solution, oxygenation did not inactivate it, and the solution was stable in air At 4° the solution could be kept several weeks without significant change [Work done under contract with the Office of Scientific Research and Development]

Isolation of a new lipoprotein (lipovitellenin) from egg yolk H L FEVOLD and ADELE LAUSTEN (by invitation) *Western Regional Research Lab, U S D A, Albany, Calif* Centrifugation of egg yolk diluted with two volumes of water results in the deposition of lipovitel in as a precipitate Ether extraction of the remaining aqueous emulsion results in a separation of three phases an aqueous phase containing the water-soluble proteins, an ethereal phase containing the fats, and a solid phase which separates between the other two Examination of this precipitate has shown it to be a lipoprotein, which has been tentatively named lipovitellenin This lipoprotein is composed of 36 to 40 per cent phospholipid (mainly lecithin) and 60 to 64 per cent phosphoprotein, this phosphoprotein has been tentatively called vitellenin

Lipovitellenin emulsifies to a stable opaque emulsion in 10 per cent NaCl but dissolves to a clear yellow solution in 10 per cent NaCl saturated with ethyl ether It may be dissolved in alkali and precipitated at neutral reaction without change in composition It is very unstable, being decomposed by alcohol or acetone, and becomes insoluble when kept in dry form at room temperature In 10 per cent NaCl saturated with ether it is stable for long periods at room temperature

Vitellenin, the protein component of lipovitellenin, is a phosphoprotein containing 0.28 to 0.3 per cent phosphorus and 0.9 per cent sulfur At neutral reactions it is insoluble in water but dissolves in alkali to a viscous solution On neutralization it is again precipitated unchanged

Phospholipid synthesis in damaged and regenerating liver EUNICE V FLOCK and JESSE L BOLLMAN *Division of Experimental Medicine, Mayo Foundation, Rochester, Minnesota* Rats maintained on four special diets, low fat low protein, low fat-high protein, high fat-low protein, high fat high protein, were exposed to carbon tetrachloride vapor for 8 hours P_{32} was injected intravenously as Na_2HPO_4 twenty-four and forty eight

hours after the beginning of the exposure. Four hours later the blood and liver were removed, extracted, and determinations of concentration and radioactivity of inorganic phosphate and phospholipid made. The acute damage to the liver did not affect the phospholipids directly. Significant decreases in concentration and rate of turnover of phospholipids in the liver were found in rats on the two high fat diets associated with an increase in the ratio of liver weight to body weight. When calculated on the basis of the whole liver and body weight the amount of phospholipid present and its rate of turnover was essentially normal. There was a tendency for the concentration of plasma phospholipid to be elevated. This was found consistently however only in the group on the high fat-high protein diet.

Approximately 70% of the liver was removed from rats maintained on the commercial diet of Friskies. One, two and four days later P^{32} was given intravenously, and the phospholipid synthesis studied. The relative activity of the hepatic phospholipids and the rate of synthesis for each gram of remaining liver was greater than normal, particularly when the liver was still small. The amount synthesized was approximately equal to that synthesized by the whole liver of a normal rat of similar size.

Isolation of brain diphosphoinositide, a new phosphatide containing inositol meta diphosphate as a constituent. JORDI FOLCH, *Rockefeller Inst., New York, and McLean Hospital, Harvard Medical School, Waverley, Mass.* Brain diphosphoinositide has been isolated from inositol phosphatide fraction of brain cephalin (J. Folch, *J. Biol. Chem.*, **146**, 35, 1942) by repeated precipitation with methyl alcohol from a 10 per cent solution of inositol phosphatide in chloroform, 12 to 18 precipitations are necessary. The product is purified by dialysis. Yield, 1 gm per kilo of fresh tissue. Diphosphoinositide contains all of the inositol present in the starting inositol phosphatide. The name has been chosen because inositol is present in the molecular as inositol meta diphosphate.

Diphosphoinositide contains 7.3 per cent P, 0.6 per cent N (mostly as NH_2-N) and (by isolation) 16 per cent inositol. It is acidic and is obtained as a calcium magnesium salt. By acid hydrolysis, inositol, H_3PO_4 , glycerol and fatty acids are obtained in ratios 1:2:1:1.

Inositol meta diphosphate has been isolated after short time acid hydrolysis of diphosphoinositide in amounts that account for 85 per cent of P and inositol present. Its structure has been established by elementary analysis, by titration with alkali, by isolation from it of inositol (95 per cent of theory) and by reaction with HIO_4 . One mol of inositol diphosphate from diphosphoinositide reacts with 2 mols of HIO_4 and produces 1 mol of

$HICOOH$. This is consistent with a meta position of the 2 phosphoryl radicals on the inositol molecule, had they been in para position, no $HICOOH$ would have been formed, in ortho position, 3 mols of HIO_4 would have been used, and 2 mols of $HICOOH$ produced.

Chemical characterization and crystallization of formaldehyde derivatives of gramicidin. H. FRAENKEL-COHAT, BEATRICE BRANDON (by invitation), and HAROLD S. OLCOTT, *Western Regional Research Lab., Albany, California.* An advantageous modification of gramicidin through formaldehyde treatment has been described (Lewis, *et al.*, *Science*, **102**, 271 (1945)). The reaction mechanism and the nature of the product have now been studied. The close agreement between the equivalents of tryptophane in gramicidin, of formaldehyde introduced, and of hydroxyl groups formed suggests that the reagent adds as methylol to the tryptophane residues. Elementary analyses and increased solubility of the derivative in aqueous alcohol agree with this hypothesis. The loss of colorimetrically detectable tryptophane, both in hydrolyzed and unhydrolyzed samples of formaldehyde derivatives, is evidence for the participation of the indole nucleus, probably at the alpha position. Further evidence was based on the reactivity of simple indoles.

Two crystalline preparations have been obtained from freshly prepared formaldehyde-treated gramicidin. Both crystallized from acetone in 30-50% yields as needles with rectangular ends, unchanged by repeated recrystallizations, they appeared alike in every respect except their melting points. The high melting product (m.p. 306-308) was obtained after the crude product had been heated *in vacuo* at 78°. Otherwise crystals melting at 205-210 were obtained, this melting point rose with time. Only fractions of intermediate melting points resulted upon crystallization of the material several weeks after its preparation. The crystalline products contained slightly fewer methylol groups than the crude, and retained slightly more of the original hemolytic activity. On the other hand, non-crystalline material recovered from the mother liquors corresponded to the unfractionated preparations in chemical and biological properties.

Use of high levels of partial acid hydrolysates of proteins intravenously in hypoproteinemic dogs. DOUGLAS V. FROST, JEAN HEINSEN, and ROBERT T. OLSEN, (introduced by D. W. MacCorquodale), *Abbott Lab., North Chicago, Ill.* Partial acid hydrolysates of casein and fibrin (White, A., and Elman, R., *J. Biol. Chem.*, **143**, 797, 1942) were analyzed for their content of essential amino acids. The tryptophane content was about one-half that of the original proteins. Deficiency of sulfuramino acids in casein hydrolysate was corrected by addi-

tion of 0.1 per cent l cysteine hydrochloride to solutions made to contain 0.7 per cent nitrogen

Adult dogs on non protein diet were made severely hypoproteinemic as determined by the plasma protein level. Intravenous injection of the test hydrolysates was made uniformly at a level of 600 mg N per kilo per day and a rate of 1.5 mg N per kilo per minute. Three-day injection periods were used as the basis for nitrogen balance studies. Hypoproteinemic dogs were injected for four 3 day periods with fibrin hydrolysate, again made hypoproteinemic for three weeks on non-protein diet and injected for four 3 day periods with casein hydrolysate. Following this, the dogs were again made hypoproteinemic and injected with fibrin hydrolysate for two 3-day periods. Studies were also made of casein hydrolysate supplemented with both cysteine and methionine.

The per cent nitrogen retained was consistently greater with fibrin hydrolysate than with casein hydrolysate, the maxima attained being 60 and 37 per cent respectively. Plasma protein and weight gain were rapid, particularly with fibrin hydrolysate. The difference in utilization of these two protein hydrolysates does not appear to be accounted for by the difference in amino acid content.

Improvements in determinations of carbon monoxide, bromsulphalein, and plasma dyes. O. H. GAEBLER and HELEN DUGGAN (by invitation) *Dept of Labys, Henry Ford Hospital, Detroit*. In palladium chloride methods for determination of carbon monoxide it is of interest that the extinction of PdCl₂ solutions in very dilute HCl is nearly constant in the region between 430 mμ and 470 mμ and increases greatly in the ultraviolet. Hence the ratio of extinction to concentration is almost equally constant whether a photoelectric colorimeter with a 440 mμ filter or a spectrophotometer is used, and very small concentrations of PdCl₂ can be determined with the latter instrument at 320 mμ. The excess of PdCl₂ is thus easily determined, after flocculating any colloidal Pd with a small amount of N HCl, diluting to a fixed volume, and filtering through a sintered glass filter tube.

Direct spectrophotometric determinations of HbCO can be made quite specific for clinical purposes as follows. Take 0.1 ml of blood with 19 ml of water and 0.2 ml of M/15 Na₂HPO₄. Add 0.8 ml of M/15 KH₂PO₄, mix, centrifugalize, and read against a water blank at 498, 562, 574, and 628 mμ. An equation for permanent use in calculating HbCO from extinctions at these four points is derived from data obtained by calibrating with solutions of methemoglobin, oxyhemoglobin, carbon monoxide hemoglobin, and sulphemoglobin, prepared from normal blood specimens of known oxygen capacity, and diluted in the above manner.

The correction for turbidity, described in con-

nection with spectrophotometric determination of T-1824 (J Lab and Clin Med 28 1494, 1943) has also been found useful in determinations of bromsulphalein (Am J Clin Path, in press) and brilliant vital red.

Biological determination of protoporphyrin. H. GILDER and S. GRANICK (introduced by L. Michaelis) *Rockefeller Inst for Medical Research, New York*. The requirement of hemin (the X factor) for the growth of *H. influenzae* is utilized as a method for the quantitative determinations of protoporphyrin and related porphyrin compounds. Other iron porphyrin compounds will support growth of *H. influenzae* but for the reduction of nitrate the vinyl groups, present in hemin and protoporphyrin, are required. Porphyrin compounds which lack iron do not support growth, some actually inhibit. These facts make possible a rather specific test for hemin and protoporphyrin.

The method consists in comparing the growth and nitrite production of organisms grown on the unknown substance with that of organisms grown on known concentrations of protoporphyrin or hemin. The nitrite is determined colorimetrically on 0.1 cc of the 18 hour culture. Comparison of this method with spectrophotometric methods shows good agreement. The biological method will detect specifically 0.01 gamma per cc of hemin whereas the lower limit for detection of porphyrins as a group by fluorescence is 0.1 gamma per cc. For detection of porphyrins by the characteristic position of the ultraviolet Soret band 1 to 5 gamma per cc are required.

The test has been used to determine the presence of traces of vinyl containing porphyrins in certain porphyrin preparations, and to confirm the identity of protoporphyrin in the Harderian gland. It is applicable for the determination of porphyrins in biological materials without the necessity for isolation.

Electrophoretic changes in the serum protein patterns of dogs subjected to various types of injury. ERLAND C. GJESSING (by invitation) and ALFRED CHANUTIN *Biochemical Laby, Univ of Virginia*. Dogs were subjected to the following types of injury: (1) dichloroethyl sulfide (mustard) and nitrogen mustards, (2) thermal injury by hot water and by dry CO₂, (3) turpentine, (4) X-ray, and (5) bone fracture. The serum was analyzed electrophoretically by the Longsworth scanning technique. The alpha globulin fraction increased in each case. There appeared to be a 48-72 hour latent period in practically all cases before the alpha globulin increased appreciably. The greatest increases in this component were observed after thermal injury, exposure to mustard vapor and subcutaneous injection of turpentine. The concentration of alpha globulin appeared to be roughly proportional to the degree of injury.

This increase apparently represented a non-specific response to tissue damage. The albumin concentration decreased.

Electrophoretic patterns together with detailed analyses of protein distribution and mobilities will be presented.

Studies of the melting points of gelatin gels
ROBERT S. GORDON, JR (by invitation) and JOHN D. FERRY, *Dept of Physical Chemistry, Harvard Medical School, Boston*. Solutions of ossein gelatin (number average molecular weight 47,000), in 0.15 M NaCl at pH 7.0, were kept at 0° for 24 hours and the resulting gels were then warmed at a rate of about 12° per hour. The melting point was taken as the temperature at which the gel, contained in the top of an inverted test tube, became fluid and fell to the bottom. It was usually reproducible to 0.1°. Measurements at various gelatin concentrations could be expressed by the equation $\ln(c - 4.7) = 141.6 - 1.18 \times 10^3/T$, where c is the concentration in grams per liter and T is the absolute temperature of melting.

Several different amino acids and related substances were added to test their influence on gelation. The melting point of a solution with 11 gram/l of gelatin without added reagent was 26.3°, with addition 1 M NaCl, 25.0°, 1 M glycine, 28.2°, 1 M proline, 27.5°, 1 M hydroxyproline, 28.0°, 1 M Na acetyl leucine, 22.9°, 1 M Na caprylate, 20.3°, 1 M Na acetyl tryptophane, no gel at 0°, 0.5 M Na acetyl tryptophane, 12.1°, 0.5 M KCNS, 20.0°. Thus the first three amino acids, all of which occur in the gelatin molecule in rather high proportions, enhance gelation slightly, whereas the molecules containing large non-polar groups together with a negative charge tend to inhibit gelation. The effect of Na acetyl tryptophane exceeds even the well-known powerful effect of thiocyanate.

Function of ferritin in regulating the absorption of iron by the gastrointestinal mucosa
S. GRANICK (introduced by L. Michaelis), *Rockefeller Inst of Medical Research, New York*. The mucosa of a 600 gram guinea pig contains ferritin only in traces present principally in the duodenum. Feeding of ferrous iron results within 4.5 hours in a marked increase in the ferritin content of the mucosa, especially in the duodenal region, this response becoming maximal 7 hours after feeding. By the 6th day after feeding, the ferritin has diminished to the level of the control animals. Feeding of ferrous iron results not only in the production of iron hydroxide micelles characterizing the iron of ferritin, but also the specific protein apoferritin is produced to which these iron hydroxide micelles attach to form ferritin. The presence of ferritin in the mucosa, its rapid increase on feeding of iron, and its relatively slower rate of disappearance, fit in with the hypothesis suggested by Hahn, Bale, Ross, Balfour and Whipple, *Jour Exp Medicine*

78:169 (1913), that ferritin may function in the regulation of iron absorption by the gastrointestinal mucosa.

Excretion of certain urinary constituents in alkaptanuria
W. KNOWITON HALL, KATRINE RAWLS and V. P. SIDFENSTRICKER (introduced by A. P. Briggs), *Depts of Biochemistry and Medicine, Univ of Georgia School of Medicine, Augusta*. Urinary analyses were made on twenty-four hour urine samples from six alkaptanuric females and three alkaptanuric males. No creatine was found in the urine samples nor were abnormal amounts of amino acids excreted, as shown by formol titration. The homogentisic acid to nitrogen ratio was relatively constant as was the ratio of total phenols (method of Folin and Denis) to nitrogen. The total organic acid content of the urine by the method of Van Slyke and Palmer in most cases was high or abnormally high and the homogentisic acid present was insufficient to account for these values. It would appear from the values obtained for excretion of total phenols, homogentisic acid and total organic acids that appreciable amounts of a phenolic organic acid other than homogentisic acid was present in the urine samples. The method of Penrose and Quastel indicated no very appreciable amounts of keto acids to be present. [Aided by grants from Merck and Co and the John and Mary R. Markle Foundation.]

Hemoglobin solutions suitable for intravenous administration
PAUL B. HAMILTON (by invitation) and LEE E. FARR, *Hospital of the Rockefeller Inst for Medical Research, New York*. A method of preparing hemoglobin solutions suitable for intravenous use was found which enabled sterile, non-pyrogenic solutions of physiological osmotic pressure and electrolyte concentration to be made rapidly and on a large scale. Ninety-five per cent of the hemoglobin in the final solutions was in the active, oxygen-carrying form. The solutions could be stored at 4°C for at least 4 months without change in appearance or without loss of oxygen-carrying capacity.

One volume of washed cells is laked with 2 volumes of pyrogen-free-distilled water. Sufficient 0.1 N HCl (0.6 to 0.8 volumes) is added to adjust the pH to 5.8, and the whole made to 4 volumes. "stroma" materials are rendered insoluble and flocculate readily. Potassium is reduced to normal plasma concentrations by exchange with sodium on treatment with Decalso (sodium zeolite). For each 100 cc of solution 3 grams of Decalso is added and mixed with swirling. The precipitated "stroma" and Decalso are removed by filtration on a coarse filter paper. Normal physiological plasma pH and bicarbonate ion concentration are restored by the addition of sodium bicarbonate. Normal plasma concentrations of Na, Ca and Mg, are restored by adding these ions as the chloride

salts The solution with dissolved salts is passed through a Seitz S-1 filter pad and the filtrate collected in sterile bottles Preparation is carried out at 4°C [*Work done under contract with the Office of Scientific Research and Development*]

Precise estimation of lysine in the van Slyke-Neill manometric apparatus with a specific decarboxylase MARTIN E HANKE *Dept of Biochemistry, Univ of Chicago* An accuracy of 1 part in 200 can be realized in analyses for free l-lysine in the manometric gas apparatus of Van Slyke and Neill, by measurement of the CO₂ liberated by a specific decarboxylase Important precautions are (1) complete preliminary removal of CO₂ from the sample to be analyzed (protein hydrolysates retain CO tenaciously), (2) addition of a minute amount (1 mg per analysis) of cysteine to prevent inhibition of enzyme action by mercury ions, (3) adjustment of the pH to 6.9 for optimum enzyme action The enzyme is prepared from cultures of *Bacillus cadaveris* as described by Zittle and Eldred¹ For analysis of solutions containing 0.5 to 5 mg l-lysine, 0.2 to 1.0 ml of a 1 to 5% aqueous suspension of the acetone-washed, dried bacterial cells in a total reaction volume of 6.5 ml and a reaction time of 30 to 120 minutes at 23 to 26°C provide conditions for the complete-decarboxylation of the l-lysine No other known substance is attacked

In the following, our values on the lysine content of proteins are expressed first as the grams lysine per 100 grams dry ash-free protein, and second (in parentheses) as the grams lysine per 10 grams of protein N Pfanstiehl casein 7.73 (8.35), Lab Co casein 8.10 (8.33), beef muscle protein (Wilson & Co) 7.62 (7.47), crystalline bovine blood albumin (Armour & Co) 11.91 (12.06), Pfanstiehl zein 0.09 (0.10)

Occurrence in foods, of an unidentified factor essential for rat growth A M HARTMAN (introduced by C A Cary) *Bureau of Dairy Industry, Agricultural Research Administration, Washington, D C* Cary et al have shown that some caseins and liver extracts supply an unidentified factor (X) essential for the normal growth of rats, that young rats may be depleted of X, and that basal diets may be constructed that are deficient in X and complete in respect to all known nutrients Using X-depleted young, the growth promoting activity of various foods has been tested, feeding these foods in such a way as not to disturb the completeness of the rations as sources of known nutrients Certain foods produced normal growth—i.e. equivalent to that of controls fed optimum amounts of X, others increased growth with increasing dose Such foods were milk, dried skimmilk, cheese, beef and pork muscle, egg yolk and certain leafy foods and feeds

These foods and feeds undoubtedly contain X, some are good sources of it The potency of egg yolk appeared to vary with the diet of the hen Other foods similarly tested gave no evidence of containing X—e.g. yeast (bakers', brewers', autolyzed), coagulated egg white, wheat bran, corn meal, linseed oil meal, soybean oil meal, wheat flour (white, enriched white, whole wheat), and when rations containing these foods were supplemented with X, growth was good—e.g. the growths (6 weeks) were, on the basal ration 116 grams and on this ration containing 45.5% of (1) enriched white flour and (2) whole wheat flour respectively 115 grams, 109 grams without X and 204 grams, 198 grams, with 10% of dried skimmilk to supply X

Renotropic effect of the anterior pituitary E HAY, P SEGUIN and M LARIVIÈRE (by invitation), and H JENSEN *Inst of Experimental Medicine and Surgery, Univ of Montreal and Dept of Research, Desbergers-Brismol Labys Selye and associates* (J Can Med A, 52, 571-82, 1945) found that administration of anterior pituitary extract causes pronounced hypertrophy and hyperplasia of the renal tubule cells as well as some increase in the diameter of the glomeruli We have undertaken studies to determine whether this effect is due to any of the known anterior pituitary principles or to a yet unknown specific renotropic factor

Assay of renotropic activity was performed in normal male rats weighing 40 to 50 grams Solutions were injected subcutaneously twice daily for 10 days On the morning following the last injection the animals were killed, bled, and the kidneys fixed and weighed The average percentage of kidney weight to body weight in the treated animals was compared with that in rats which had been injected with the same volume of 0.85% sodium chloride solution

We have found that administration of highly purified thyrotropic preparations produces a pronounced renotropic effect in normal and hypophysectomized rats A small increase in proportionate kidney size was observed on administration of adrenocorticotrophic preparations On the other hand administration of lactogenic, gonadotropic or growth preparations did not elicit any renotropic effect However, it cannot be concluded from these observations that the renotropic response of a crude anterior pituitary extract is due solely to the presence of the thyrotropic principle, since small doses of thyroxine synergize the response of crude anterior pituitary extracts and since the renotropic effect of crude anterior pituitary extracts can be elicited, though to a smaller degree, in thyroidectomized rats

Studies in steroid excretion H HIRSCHMANN (introduced by Ralph I Dorfman) *Dept of Medicine, Western Reserve Univ, and the Lakeside Hospital, Cleveland* The examination of the urine

¹ C A Zittle and N R Eldred J Biol Chem 156 401 (1944)

of a boy with adrenocortical carcinoma which previously had yielded Δ^5 -androstenediol-3(β), 16, 17, Δ^5 -androstenediol-3(β), 17(α), and Δ^5 -pregnenediol-3(β), 20(α) has furnished two additional compounds not previously described as constituents of human urine. One of these is an alcohol melting at 181–184° which forms an acetate (m p 143–144.5°). The analyses indicate the composition $C_{27}H_{46}O \pm CH_2$ for the parent compound. The 3 double bonds suggested by this formula are present in a benzenoid ring as was shown by the specific absorption of this substance in the ultraviolet ($\lambda_{max} = 268$ m μ , $\log \epsilon = 2.56$). The spectrum is characteristic of a benzenoid ring occupying a central rather than a terminal position in the ring system. The second substance (m p 293–299°) analyzed for $C_{27}H_{46}O_2$. It forms a monoacetate (m p 273–278°) and a mono-oxime (m p 269–272°). [This investigation was supported by a grant from the Commonwealth Fund.]

Diet and calcium phosphate deposits in guinea pigs. A. G. HOGAN and W. O. REGAN (by invitation) *Dept of Agricultural Chemistry, Univ of Missouri, Columbia*. A typical basal diet was composed of casein 20, sucrose 36 or 35, cellulose 15, lard 10, salts 4 or 5, and dried brewers' yeast 15. Vitamins A, D, E, and K were dissolved in the lard. Salt mixture A was included at a level of 4 per cent, and 4 grams contain 0.2 grams of phosphorus. Salt mixture B was included at a level of 5 per cent and 5 grams contain 0.6 grams of phosphorus. The two salt mixtures contain approximately the same amount of calcium. When the diet contained salts A the animals grew fairly well and there were few abnormalities. When the diet contained salts B practically all of the animals developed localized deposits of calcium phosphate. Usually these are first observed on the soles of the feet or on the toes, and they resemble a pinhead size infection. Examination discloses the presence of innumerable microscopic crystals of calcium phosphate. The deposits may also appear on any of the long bones, on the ribs, spinal column, on the superficial muscle surfaces, and on various internal organs. Usually they do not appear until the animals have been on the experimental diet for 6 months or more. With one exception, the deposits have not appeared in animals that consumed diets of natural foodstuffs, even though the diet contained as much phosphorus as did the experimental diets which included salts B.

Use of the "counter-current distribution" technique for the isolation of biologically active principles. GEORGE H. HOGEBOM (by invitation) and LYMAN C. CRAIG *Rockefeller Inst for Medical Research, New York*. The "Counter-Current Distribution" technique¹ was found to provide a relatively simple method for separation, purification,

and characterization of several closely related substances which are produced by *Aspergillus ustus* and inhibit the growth of mycobacteria.² A crude preparation obtained by ether extraction of the *aspergillus* and its culture medium exhibited acidic properties and was soluble both in alkaline buffers and in organic solvents. When this crude antibiotic was subjected to a 24 plate counter-current distribution in a machine similar to that described by Craig in the system cyclohexane/0.2 molar $Na_2P_2O_7$ buffer, pH 8.31, a pure crystalline, growth inhibiting substance (Mp 185–7°, C 53.37, H 3.64, Cl 22.63, probable formula $C_{21}H_{17}Cl_3O_6$) was isolated from the tubes forming a symmetrical band. The tubes of a second asymmetrical band contained a non-crystalline mixture, also antibiotically active, which migrated only slightly with the buffer. Separation of the components of the asymmetrical band was easily attained by increasing the alkalinity of the pyrophosphate to 8.66, using the same organic phase, and again employing a 24 plate run. This procedure yielded a second crystalline active substance (Mp 215–16°, C 58.02, H 4.19, Cl 16.84, probable formula $C_{21}H_{15}Cl_3O_6$) and a third, partially crystalline fraction now under study. The two pure compounds and the third impure fraction showed approximately equal antibiotic activity, completely inhibiting the growth of *Mycobacterium ranac* at dilutions of 1/100,000 to 1/300,000.

Thiamine requirement of infants. L. EMMETT HOLT, JR., and ANTHONY A. ALBANESE (by invitation), ROSA LEE NEMIR, KATHERINE C. KETRON, and SELMA SNIDERMAN *Dept of Pediatrics, New York Univ*. Although considerable information has been obtained in regard to the thiamine requirement of the adult, based on various experiments with purified diets, exact information as to the requirement of the infant has not been available.

A group of infants were placed on a purified diet in which B vitamins were supplied as a mixture of pure substances. The quantity of thiamine was reduced until the minimal level of urinary excretion of this factor was obtained. Previous studies by Najjar and Holt (*J A M A* 123:683, 1943) carried out in adolescents and young adults had shown that minimal urinary excretion values for this factor were obtained with a thiamine intake two to three times as high as that which led to deficiency symptoms. It was therefore felt that in the infant an intake sufficiently low to barely induce the minimal excretion level would likewise afford protection against deficiency symptoms by a similar margin.

By gradual adjustments of the thiamine intake it was found that the minimal urinary excretion in infants of 12 to 16 pounds in weight could be attained by reducing the thiamine intake to 14

¹ Craig, L. C., Golumbic, C., Mighton, H., and Titus, E., *J Biol Chem*. In Press.

² Kurung, J. M., *Science* 102:11 (1945).

to 18 mg per day. Intakes of this order of magnitude were maintained for several months without any clinical evidences of deficiency.

Cytochrome C-cyanide complex B L HOR-ECKER and ARTHUR KORNBERG (introduced by Harry D Baernstein) *National Inst of Health, Bethesda, Md*. In studies involving the reduction of cytochrome C by the succinic dehydrogenase system, it was observed that in the presence of cyanide there is a progressive decrease in the amount of reducible cytochrome C. This confirms observations previously reported by Potter¹.

The kinetics of the reaction

$\text{Cytochrome C} + \text{CN}^- \rightleftharpoons \text{Cyancytochrome C}$
have been studied enzymatically and spectrophotometrically. At 27°C and pH 7.3, the equilibrium constant has a value of 2×10^{-6} . The reaction velocity constant for the formation of the complex is 7×10^2 . The failure of enzymatic reduction to reverse the formation of complex is therefore attributable to the very slow rate of dissociation. $\text{Na}_2\text{S}_2\text{O}_4$ reduces the complex with the formation of free reduced cytochrome C.

The change in spectrum of oxidized cytochrome C in the presence of cyanide as observed by Potter has been confirmed. In addition concentrated solutions of cytochrome C show an absorption band at 6900 Å which disappears on addition of cyanide or with enzymatic reduction. The relation of this band to cytochrome C is discussed.

Factors affecting the levels of lactic acid and pyruvic acids in the blood M K HORWITT, O KREISLER (by invitation) and RAY D WILLIAMS *Biochemical Research Lab, Elgin State Hospital, Dept of Biological Chemistry, Univ of Illinois College of Medicine, Chicago, and Dept of Medicine, Washington Univ, St Louis*. In the course of long term observation of human subjects on a diet considerably restricted with respect to thiamine and riboflavin, variations were observed in values for lactic and pyruvic acid. These variations were independent of those which occurred as a result of dietary restrictions. Furthermore, they occurred not only in subjects on the restricted diet, but also in subjects who were serving as controls and received the same diet supplemented with yeast to raise the intake of thiamine and riboflavin. Individuals showed a definite range within which their levels of lactic and pyruvic acid varied. This applied not only to the basal levels of these substances, but also to the levels noted after giving glucose and after exercise.

Environment apparently accounted for these variations. On a given day the results on every subject tested would be higher than on another day. The phenomenon has been shown not to be an artefact, as was at first suspected. It has been studied

for a period longer than two years in more than thirty-five subjects.

Acid-base reactions of quinoline and acridine derivatives J LOGAN IRVIN and ELINOR MOORE IRVIN (by invitation) *Dept of Physiological Chemistry, The Johns Hopkins University, School of Medicine, Baltimore*. Apparent acid dissociation exponents ($\mu = 0.1, 30^\circ$) for various derivatives of quinoline and acridine were determined potentiometrically and spectrophotometrically with good agreement. Values of pK'_{a1} (ring nitrogen) for quinoline and plasmochin are 4.28 and 3.46, respectively. The value of pK'_{a2} (diethylamino group) for plasmochin is 10.2. A second reversible acid-base reaction involving the aromatic nucleus of plasmochin was determined spectrophotometrically in concentrated solutions of strong acids (mid-points at concentrations of 3.6 N HCl and 5.6 N H_2SO_4 , respectively). This reaction probably involves the secondary amino nitrogen. In sulfuric acid from 20 N to 35 N a small change in spectrophotometric absorption by plasmochin occurs, and there is a striking increase in fluorescence which can be applied in determining plasmochin.

In a series of 4-amino quinolines with identical side chains (1-methyl-4-diethylamino-butyl-) attached to the amino group, the distinctive substituents and the corresponding values of pK'_{a1} (aromatic nuclei) for the compounds are: 6-methyl-8.75, 7-chloro-8.03, 2-methyl-7-chloro-8.51, 3-methyl-7-chloro-7.28. pK'_{a2} (diethylamino group) is 10.2 in each case. A second proton is accepted by the aromatic nucleus in very strongly acid solutions (20–35 N H_2SO_4).

For the 9-amino acridines, as well as for the 4-amino quinolines, the effects of substituent groups on basicity appear to be related to the relative electronegativities of the groups and to the relative symmetry of substitution.

In an homologous series of 2-methoxy-6-chloro acridines with side chains of the type, $-\text{NH}(\text{CH}_2)_n\text{N}(\text{C}_2\text{H}_5)_2$, substituted in the 9-position, the values of pK'_{a2} bear an inverse linear relationship to the corresponding values of $1/n$.

Rate of urinary excretion of ascorbic acid, thiamine, riboflavin and N¹-methyl-nicotinamide and the effects of diuresis, alkalosis, acidosis and ingestion of food ROBERT E JOHNSON *Fatigue Lab, Harvard Univ, Boston, Mass*. The rate of excretion of vitamins in the urine has been widely studied in relation to dietary deficiency, but there has been little systematic observation on other possible causes of variation. We have studied the rates of urinary excretion of ascorbic acid, thiamine, riboflavin and N¹-methyl-nicotinamide in 12 young men living on similar adequate diets. During separate mornings the effects were studied of ingesting enough water to produce a significant diuresis, of ingesting sodium bicarbonate, of ingesting

¹ Potter V R, *J Biol Chem* 137 13 (1941)

ammonium chloride and of eating breakfast. In each experiment six of the subjects were used as controls and during the course of the study all combinations of the factors listed above were tested. No significant effect on the rate of excretion of any of the four vitamins was observed (a) when the urinary pH was raised to 7.5 by ingestion of sodium bicarbonate, (b) when the urinary pH was lowered to 5.0 by ingestion of ammonium chloride, (c) when breakfast was eaten. In contrast, ingestion of water enough to cause an excretion of 200 ml of urine per hour resulted in increased rates of excretion of thiamine, riboflavin and N-methylnicotinamide, but had no effect on the excretion of ascorbic acid. Diuresis up to 100 ml of urine per hour had no effect on the excretion of any of the four vitamins. Controls produced about 40 ml of urine per hour, and at rates below 25 ml per hour, the excretion of all four vitamins decreased.

Analysis of basic organic compounds in biological tissues. 6 **Ultraviolet spectrophotometry.** EDWARD S. JOSEPHSON (by invitation), SIDNEY UDENFRIEND (by invitation), and BERNARD B. BRODIE. *Goldwater Memorial Hospital and New York Univ., New York.* Spectrophotometry using the ultraviolet lacks the sensitivity of the methods of assay previously described, but it is useful as a final means of assay in certain instances, as an aid in developing procedures which eventually involve other principles of assay, and as an adjunct in the examination of specificity.

Ultraviolet spectrophotometry has been utilized in the design of methods for organic bases in plasma at concentrations of about 1 mg./L. A recent simple micro-adaptation of the Beckman spectrophotometer makes it probable that the sensitivity can be increased several times. The method as applied to quinine is as follows. Quinine is isolated from alkalized plasma by extraction into acid-washed ethylene dichloride and is then returned to 0.1 N H_2SO_4 . The drug is assayed spectrophotometrically at 250 m μ . Glassware used in the acid extraction and quartz cuvettes must be chromic-acid cleaned. Reagents and normal plasma run through the procedure negligible absorption between 240-400 m μ .

Preliminary information from spectrophotometric analysis of biological material is useful in developing an analytical procedure which will ultimately utilize another method of final assay. Optimal conditions for the extraction of a drug from biological material may be worked out simply and quickly using a variety of combinations of pH and organic solvent with the drug at concentrations measurable with this technique. This information is essential in determining the general form of an analytical procedure before information is available on the sensitivity which will be required. Spectrophotometric study of apparent drug measured in an analytical procedure is commonly useful in evaluat-

ing the extent to which an analytical procedure has specificity.

Maintenance of nitrogen balance on low nitrogen and low caloric intakes. CHARLES F. KADE and JIAN HOUSTON (by invitation), and MELVILLE SALLUN. *Federick Stearns Division, Sterling Drug Inc., Detroit.* The effects of three different diets, wherein the sole source of nitrogen consisted of a metaprotein of lactalbumin, were studied on female dogs with respect to nitrogen balance.

In the first series of experiments, the nitrogen and caloric intakes were 90 mg. and 80 calories per kilo of body weight, respectively. On this diet the animals were maintained for several months in good positive nitrogen balance. Gain in weight was observed. These animals remained in positive nitrogen equilibrium even when the caloric intake was reduced to 40 calories per kilo of body weight. However, they excreted more nitrogen than they took in when the calories fed were less than 40 per kilo of body weight.

In the second series, the dogs received 500 mg. of nitrogen of the metaprotein per kilo of body weight and their caloric intakes were gradually reduced from 80 to 20 calories per kilo of body weight. On 20 calories per kilo the caloric intake was almost entirely derived from the metaprotein in the diet. The animals were maintained in nitrogen equilibrium.

In the third group the dogs were first kept on a diet of 150 mg. of nitrogen per kilo of body weight. The caloric intake was gradually reduced from 80 calories to 20 calories per kilo. The animals were in negative nitrogen balance on 20 calories per kilo but returned to positive nitrogen balance when the caloric intake was raised to 30 calories per kilo.

Effect of splenectomy on the anemia of cholesterol fed guinea pigs. BARBARA KENNEDY (by invitation) and RUTH OKEY. *Dept. of Home Economics, Univ. of California, Berkeley.* Grossly enlarged spleens are always present in guinea pigs made anemic by cholesterol feeding. Other indications of the hemolytic nature of this anemia are hyperplastic bone marrow, increased fragility of erythrocytes, fatty livers and high serum bilirubin (*J. Biol. Chem.* 156:179, 1944).

In order to determine the extent to which splenic activity affected the development of the anemia, 15 guinea pigs were splenectomized. Thereafter 2 were fed abrain stock diet, 6 a "basal" diet containing 20 per cent casein, 10 per cent yeast, and 12.5 per cent fat, and 7 were given this "basal" diet plus 1 per cent cholesterol.

The splenectomized animals given the stock diet appeared normal. Tolerance for the "basal" diet was somewhat lessened by splenectomy. Growth was poor and there were some indications of a red cell destruction slightly greater than normal. Splenectomized animals given the basal diet with 1

per cent cholesterol had erythrocytes counts which fell to approximately 3 million in 50 to 60 days. Livers were markedly fatty and serum bilirubin was high. Anemias were fully as severe as in the intact animals on the same diet.

This would indicate that the enlargement of the spleen does not produce, nor does its removal prevent the anemia of cholesterol fed guinea pigs.

Effect of hemin proteins on soybean lipoxidase
MARIAN W. KIES (introduced by A. K. Balls)
Bureau of Agricultural and Industrial Chemistry, U. S. Dept. of Agriculture, Albany, California. In a study of hemin catalyzed fat oxidation, Haurowitz¹ has reported that the so called essential fatty acids are particularly susceptible to this type of oxidation. Balls, et al.,² noted the same specificity for soybean lipoxidase. Since the substrate specificity of the two appeared to be similar, a study of their relative actions was undertaken.

Purified soybean lipoxidase and crystalline bovine hemin were compared as fat oxidation catalysts under identical experimental conditions. Hemin is more effective, weight for weight, than our lipoxidase preparation but, unlike the latter, is completely ineffective if the reaction mixture contains 10 per cent acetone. Haurowitz (1) has shown that hemin is eventually destroyed during the catalytic process. In our experiments, oxygen absorption curves indicate that lipoxidase is even more readily inactivated.

The effect of hemin and various hemin proteins on lipoxidase activity was investigated. Hemin and cytochrome inhibit lipoxidase completely whereas catalase, peroxidase and hemoglobin do not. The effect of cytochrome is apparently a property of the ferric form since reduced cytochrome is readily oxidized (as a co substrate) by lipoxidase plus linoleic acid. The latter reaction depends on the presence of both unsaturated fat and enzyme, and is not inhibited by 0.02 M NaCN. However, once the oxidized cytochrome is formed no further enzymatic action can be detected.

Distribution of intravenously injected fructose and glucose between blood and brain
J. RAYMOND KLEIN and RUTH HURWITZ (by invitation) *Dept. of Psychiatry, Illinois Neuropsychiatric Inst., Univ. of Illinois College of Medicine, Chicago*. The concentrations of fructose and glucose in blood and cerebral hemispheres of cats under Dial anesthesia, determined at intervals after intravenous injections of these sugars, are such as to indicate that the rate of transfer of fructose from blood to brain is considerably less than that of glucose. The data of Kerr and Ghantus (*J. Biol. Chem.*, 116:9 (1936)) indicate that overt symptoms of hypogly-

cemia appear in dogs when the concentration of glucose in brain is below 30 mg per 100 gm and below 12 mg in rabbits. The concentrations of fructose found in brain, e.g., 5 mg per 100 grams of blood-free tissue 5 minutes after a dose of 2 grams per kg and 43 mg per 100 grams 32 minutes after a dose of 2.9 grams per kg, indicate that the rate of transfer of fructose from blood to brain is insufficient to provide a concentration that might be expected to relieve or prevent the effects of hypoglycemia.

Effect of over-nutrition on ketosis
ALFRED E. KOEHLER and ELSIE HILL (by invitation) *Santa Barbara Cottage Hospital and The Sansum Clinic, Santa Barbara, California*. Over-nutrition is usually listed as a cause of diabetic coma. We have verified the reported findings that excessive carbohydrate feeding does not induce ketosis. In ten controlled diabetic subjects on a maintenance 2 to 1 diet, averaging 60 units insulin, an additional 1000 calories of fat was given daily for periods varying from 2 weeks to 3 months. This usually represented the maximum that they could eat. The urine and blood ketone values did not increase. Stool analysis showed that the fat was nearly completely utilized except in 2 cases during a period of diarrhea. The gastrointestinal upset in these 2 cases immediately produced a definite ketosis and the experiments had to be discontinued.

Our experiments indicate that over-nutrition with carbohydrate or rats in controlled diabetes does not produce ketosis. Associated systemic disturbances, probably altering liver function may, however, produce acidosis.

Rate of the Liebermann-Burchard cholesterol color reaction
ALFRED E. KOEHLER and ELSIE HILL (by invitation) *Santa Barbara Cottage Hospital and The Sansum Clinic, Santa Barbara, California*. The rate of the cholesterol color reaction was measured by means of a photoelectric colorimeter in conjunction with a water bath maintained at 25°C. The usual procedure of mixing the reagents at the start of the reaction was unsatisfactory because of the heat of reaction causing a rise of 1.5°C even in a well stirred water bath.

The procedure adopted was to add 0.1 cc sulfuric acid and 1.0 cc acetic anhydride to 4 cc chloroform and this was added to the cholesterol in 1 cc chloroform after each had reached 25°C. This method speeds the color development because the preliminary incubation of the chloroform acid mixture completes this phase of the reaction.

Commercial cholesterol purified and 6 times recrystallized had a 50 per cent color development in 4 minutes and 23 seconds while blood serum total cholesterol developed 50 per cent color in 2 minutes 27 seconds and serum esters after digitonin separation gave half color in approximately the same time.

¹ Haurowitz, F., Schwenn, P., and Yenson, M., *J. Biol. Chem.* 140:353 (1941).

² Balls, A. K., Axelrod, B., and Kies, M. W., *J. Biol. Chem.* 149:491 (1943).

Cholesterol prepared from serum and recrystallized 8 times had approximately the same rate of reaction for both total and esters

The Liebermann reaction is diphasic and color development is dependent upon the completion of the chloroform-acid-anhydride reaction

Purified serum cholesterol is a different form of cholesterol than that usually used for standards. The latter may have been altered in the process of manufacture

Total cholesterol and esters have approximately the same rate of color reactions

Amino acids in the production of granulocytes in rats ARTHUR KORNFELD (introduced by W H Sebrell) *Division of Physiology, National Inst of Health, Bethesda, Md* Severe granulocytopenia and anemia are noted in high incidence when weanling rats are fed protein-free diets. Treatment of the granulocytopenia with synthetic *L. casei* factor (L C F, "folic acid") resulted in a slight average increase in granulocyte count. Administration of diets containing 18 to 50% casein in the absence of L C F was ineffective. However, the combined administration of L C F with casein or with egg white was highly effective. The average granulocyte count rose from 300 cells per cu mm to a level of 4000

A mixture of the 10 "essential" amino acids successfully replaced casein or egg white. Of these 10 acids, none was dispensable except arginine which appeared to be essential in only about half of the animals. Findings with amino acid supplementation of modified or deficient proteins substantiated findings with mixtures of purified amino acids. Thus, oxidized casein (Toennies, *Jour Biol Chem* 145 667) promoted granulocyte production only when supplemented with methionine and tryptophane. Dried plasma was ineffective unless supplemented with isoleucine

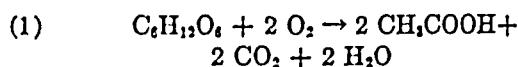
In the production of erythrocytes, preliminary data also indicate that a mixture of the 10 "essential" amino acids can largely replace casein. Methionine and tryptophane appear to be indispensable as indicated by findings with oxidized casein

The administration of the "essential" amino acid mixture at an 18% dietary level to the protein-depleted rats resulted in a high mortality. Similar but less pronounced toxicity followed the feeding of a 50% casein-containing diet

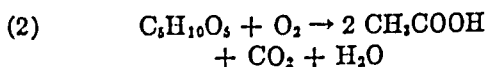
Edema and low serum protein concentrations were noted in some protein-depleted rats

On the mode of action of penicillin L O KRAMPITZ (by invitation) and C H WERKMAN *Dept of Bacteriology, Iowa State College, Ames* An inhibitory effect of penicillin on *Staphylococcus aureus* was demonstrated which apparently involves the metabolism of nucleotides or nucleic acids

Twenty mgs lyophilized cells (or freshly harvested cells) in phosphate buffer, pH 7.0, exhibited a small and constant rate of oxidation of the endogenous substrates for from four to six hours, after which there was a gradual positive acceleration of activity which attained a level of approximately 250 μ l O₂/hour after six to eight hours. This acceleration is totally inhibited by 400 units crystalline penicillin G sodium/ml. Autoclaved penicillin was not inhibitory. The R Q during the rapid phase of oxidation was 1.0, and acetic acid accumulated



Equation (1) satisfies these conditions, however penicillin had no effect on the reactions concerned. Nor was the release of glucose from polysaccharides etc. which could be subsequently oxidized inhibited by penicillin



Equation (2) represents the oxidation of pentoses to acetic acid with a R Q of 1.0. No inhibition of the oxidation of ribose or its phosphate esters was detected. The possibility that ribose from cellular nucleic acids was oxidized and that the liberation was inhibited by penicillin was investigated

When yeast sodium nucleinate was added to a suspension of cells, a rate curve exhibited similarities to the endogenous curve. The acceleration, however, appeared two to four hours earlier, and the maximum oxidation was considerably higher (425 μ l O₂/hr) and was maintained a longer period. 400 units crystalline penicillin was completely inhibitory

Quinine, avitaminosis, and motility GRANVILLE C KYKER, MILDRED McEWEN, E MCG HEDGPETH, and VIOLET YOUNG (introduced by James C Andrews) *Dept of Biological Chemistry and Nutrition, School of Medicine, Univ of North Carolina, Chapel Hill* Although intestinal motility and absorption are decreased by a deficiency of vitamin B₁ and certain other members of the B-complex, previously reported results indicate that intestinal motility increases when B complex deficient rats receive quinine. A radiographic study confirms this conclusion

Eight young rats, equally divided according to sex, were caged individually and studied radiographically at 15, 60, and 120 minutes after each of five barium meals which were administered respectively on the following experimental days 1, 3, 23, 25, and 32. Food and water were withheld one day before each meal. The first and third meals consisted of a barium suspension while the second, fourth, and fifth contained quinine also. An adequate diet preceded the first two meals and

thereafter a diet free of vitamin B complex was provided. A moderate avitaminosis prevailed when the third and fourth meals were administered and a severe avitaminosis had developed when the fifth meal was administered.

The greatest difference in motility appears in the fifteen minute studies. Quinine and avitaminosis B complex depress motility slightly when acting separately but increase motility greatly when imposed simultaneously. This increase in motility is greater when the avitaminosis is more severe. [Supported by a grant from the Samuel S. Fels fund.]

Effect of level of thyroid activity on response of ovariectomized rats to estrone. WRIGHT LANGHAM (by invitation) and R. G. GUSTAVSON, *Univ. of Colorado, Denver*. Daily subcutaneous injections of ovariectomized rats with 1, 2, and 3 γ of di-thyroxin per gram of body weight for periods of 3, 6, and 10 days greatly decreased their sensitivity to a constant dose of estrone. Response was determined by vaginal smears. Weight loss and decreased sensitivity to estrone were approximate logarithmic functions of the level and duration of thyroxin dosage. Response returned to normal in 28 days after thyroxin administration.

Thyroparathyroidectomy increased the sensitivity of ovariectomized rats to a constant dose of estrone, thirty-eight days after operation. 76 per cent more animals responded than among unoperated controls. The increased sensitivity was partially corrected by 3 daily injections of 0.1 γ of thyroxin per gram body weight. The rat unit of estrone (amount required to produce estrus in 50 cent of a large group of animals) was 0.86 γ for thyroparathyroidectomized castrates, 1.33 γ for control castrates and 2.50 γ for castrates rendered hyperthyroid by 6 daily injections of 2 γ of di-thyroxin per gram body weight.

Ovariectomized rats rendered hypothyroid by continually administering thiourea in drinking water showed a marked immediate decrease in sensitivity to estrone followed by a gradual increase, becoming as sensitive after 56 days as thyroparathyroidectomized castrates.

Thiourea was acutely toxic to mature rats of California and Yale strains but not to immature animals. Seventy per cent of mature animals receiving 2.5 mg of thiourea orally or intraperitoneally died within 24 hours. Death resulted from suffocation, the plural cavity filling with fluid.

Partial purification of thymonucleodepolymerase. MICHAEL LASKOWSKI, *Dept. of Biochemistry, Marquette Univ. School of Medicine, Milwaukee*. With the aid of the recently described method for the determination of thymonucleodepolymerase (Arch. Biochem. 7, 465, 1945) partial purification of this enzyme was achieved. Fresh

hog pancreas cooled to 0°C (or frozen pancreas) was blended with an equal volume of 0.2 N H₂SO₄ in the Waring blender, and centrifuged. The liquid was collected, adjusted to pH 7, treated with Panther Creek bentonite (7.5 gm per each 100 cc of fluid), and centrifuged. The liquid was collected, cooled to 0°C and treated with 2 volumes of cold methyl alcohol. This precipitate could be preserved by drying, but in the process a loss of 50% of activity occurred. The product is free from phosphatase, but contains some ribonuclease. If instead of drying, the precipitate obtained with methyl alcohol is taken up in borate buffer, it can be further purified by fractional precipitation with methyl alcohol at low temperature. The best preparation so far obtained had 100 times higher potency per mg of protein than the original pancreas. The enzyme is strongly inhibited by NaCl in concentrations greater than 0.5 molar. Thymonucleodepolymerase thus obtained converted most of the phosphorus of thymonucleic acid to a form soluble in 75% trichloroacetic acid. [Aided by a grant from the John and Mary R. Markle Foundation.]

Percutaneous penetration of mercury in the rat. E. P. LAUG, and (by invitation) E. A. VOS, E. J. UMBERGER and F. M. KUNZE, *Division of Pharmacology, Food and Drug Administration, Federal Security Agency, Washington, D. C.* The quantity of mercury which penetrates the skin after a short exposure to various types of mercurial ointments may be so small as to escape detection in urine and blood. However, the liver and kidneys, to the exclusion of all other tissues examined, show the property of concentrating or storing mercury, even when the amounts in blood are extremely minute. It has been found that the concentration of mercury in liver and kidneys, following cutaneous inoculation are a relative measure of the amounts which have penetrated the skin and entered the circulation. On the basis of this finding, a number of factors have been examined which appear to influence the penetration of mercury through the skin from inoculated ointment. (1) The type of mercury compound and its physical state of subdivision. (2) The physical and chemical composition of the vehicle. (3) The physical and chemical treatment of the inoculated skin area.

Further studies on the rôle of biotin in mammalian tissue metabolism. JOHANNA M. LEE (by invitation), WILLIAM H. SUMMERSON and VINCENT DU VIGNEAUD, *Dept. of Biochemistry, Cornell Univ. Medical College, New York*. The finding that biotin is concerned in the aerobic utilization of lactate by surviving rat liver tissue (Summerson, Lee and Partridge, Science, 100: 250, 1944) has been confirmed and amplified by further study. Studies on liver slices from biotin-deficient rats in the presence of a variety of substrates have failed to indi-

cate that biotin influences the metabolism of substances other than lactate. The effect of added biotin in increasing the rate of utilization of lactate by biotin-deficient liver slices is abolished by poisoning with arsenite, which completely inhibits lactate utilization by liver slices.

Studies on the dehydrogenase activity of liver homogenates from normal rats have shown that an inhibition of 50 per cent or more in the rate of hydrogen transfer is obtained in the presence of small amounts of avidin, a protein which combines specifically with biotin. This inhibition is completely reversed by an excess of added biotin. These findings indicate a possible rôle of biotin in hydrogen transport, our present evidence indicates that a lactic dehydrogenase is probably concerned.

Histamine oxidase L F LOLOIR (by invitation) and D E GREEN *Depts of Medicine and Biochemistry, College of Physicians and Surgeons, Columbia Univ.* Histamine oxidase of pig kidney has been purified by acetone precipitation of the minced tissue, fractionation with ammonium sulfate, adsorption on tricalcium phosphate and alumina γ , isoelectric precipitation and finally electrophoretic separation. The final product appears to be a colorless protein. The claim by Zeller¹ that the enzyme is a flavoprotein is thus not substantiated. There was no evidence of a dissociable prosthetic group under the conditions of the isolation procedure. The most purified and presumably homogenous product obtained by electrophoretic separation catalysed the oxidation of a whole series of aliphatic and aromatic diamines in addition to histamine whence it may be concluded that histamine oxidase is identical with the so-called diamine oxidase.

Zinc is present in the enzyme at all stages of purification but since the concentration of zinc per unit of enzyme activity declines progressively during the purification, there is no evidence that zinc is present other than as an impurity in the final product. No significant amounts of iron, manganese or copper were found. The available evidence suggests that the prosthetic group of histamine oxidase is not identical with any hitherto described. [Supported by a grant from the John and Mary Markle Foundation.]

Iodination of tyrosine groups in "Regenerated" serum albumin CHOH HAO LI *Inst of Experimental Biology, Univ of California, Berkeley*. From the rate of iodine up-take in human serum albumin and pepsin (J A C S 67 1065, 1945) the behavior of tyrosine groups in these native proteins was shown to differ from that found in denatured state. Further data on the iodination rate of the

"regenerated" serum albumin have been obtained and are reported herein.

When a two per cent human serum albumin solution in 7.1 *m* urea (pH 7.0 phosphate buffer) stood at 25°C for 24 hours, the protein recovered after the removal of urea by dialysis was assumed to be "regenerated" according to Neurath, Cooper and Erickson (J Biol Chem 142 249, 1942). In pH 5.70 acetate buffer, both the rate of iodine decrease and the extent of iodine up-take in "regenerated" albumin solutions were identical with that found in the native protein, i.e. only 50 per cent of the phenolic group in the "regenerated" serum albumin were available for iodination.

If the phenolic groups in the extended form of the denatured protein return to a somewhat different arrangement in the condensed configuration after the removal of the denaturing agent, a different iodination rate might occur in the "regenerated" albumin. Since the same rate of iodination was observed in the "regenerated" protein, it is evident that either the phenolic groups resume their former specific relative positions characterizing the native state or at any rate steric arrangement permits the same iodination kinetics as in the native molecule.

Sulfur amino acids in growth and adrenocorticotrophic hormones CHOH HAO LI *Inst of Experimental Biology, Univ of California, Berkeley*. Growth and adrenocorticotrophic hormones were isolated from ox and sheep pituitaries respectively by the procedures previously described (J Biol Chem 149 413, 1943, 159 353, 1945). The colorimetric method of McCarthy and Sullivan (J Biol Chem 141 871, 1941) was used for the determination of methionine, while the cystine content was obtained by the method of Sullivan, Hess and Howard (J Biol Chem 145 621, 1942). The protein hormone samples were digested with 6 *m* HCl at 115°C for a period from 11 to 40 hours. The digested mixtures were decolorized with charcoal (Norit), filtered and diluted to proper concentrations. The Cenco photometer was employed for color comparisons.

From nine determinations on four samples of growth hormone, average values of 3.06 ± 0.08 per cent methionine and 2.25 ± 0.05 per cent cystine were obtained, the total sulfur content in the hormone as computed from these values is found to be 1.25 per cent.

Adrenocorticotrophic hormone contains 1.93 ± 0.02 per cent methionine and 7.19 ± 0.14 per cent cystine from ten determinations on three hormone samples. The computed sulfur content in adrenocorticotrophic hormone amounts to 2.32 per cent.

It may be recalled that the sulfur content in growth and adrenocorticotrophic hormones as determined by the Carius method as previously reported, is 1.30 and 2.30 per cent respectively and

¹ Zeller, E. A., Stern, R., and Wenk, M., *Helv. Chem. Acta* 23 3 (1940).

that both hormones contain no cysteine. Thus, within the limits of experimental error, the methionine and cystine content accounts for the total sulfur in the growth and adrenocorticotrophic hormones.

Specificity of pectinesterase or higher plants
HANS LINEWEAVER, and (by invitation) EUGENE F. JANSEN, L. R. MACDONNELL and ROSIE JANG, *Western Regional Research Lab., U. S. D. A., Albany, Calif.* Extension of the work of other investigators on the specificity of pectinesterase indicates that only esters of polygalacturonic acids are hydrolyzed rapidly by pectinesterase. Ethyl and methyl polygalacturonides, prepared (with some degradation) by refluxing pectic acid in acidified alcohol, were hydrolyzed by purified orange-flavado pectinesterase at about 6 and 60 per cent, respectively, of the rate at which this enzyme hydrolyzed pectin. The methyl esters of a polymannuronide (alginic acid) and of the two monomers (methyl-D galacturonate and methyl- α -methyl-D galacturonate) were hydrolyzed at less than 0.02 per cent of the rate of pectin hydrolysis. Of some twenty non-uronic esters tested (including glycerides) none was hydrolyzed by crude orange pectinesterase at more than 2 to 3 per cent of the rate of pectin hydrolysis. Some if not all of this activity was due to enzymes other than pectinesterase as shown by tests with purified orange pectinesterase and with unpurified tomato pectinesterase. Pectinesterase, therefore, appears to be highly specific quantitatively (and perhaps qualitatively) for polygalacturonide esters (derivatives of pectin substances), in contrast with the view of those investigators who have considered pectinesterase to be not especially specific.

The reaction mixture consisted of 0.5 per cent substrate, 0.15 *M* salt, and enzyme. The minimum detectable activity was 0.02 per cent of the activity on pectin. The rates at which it was necessary to add 0.02 *N* alkali to maintain pH 6.8 in the unbuffered reaction mixture was the measure of activity. For substrates tested at pH 4.5 the activities, if detectable, were less than at pH 6.8.

Report on a coenzyme for acetylation FRITZ LIPMANN and NATHAN O. KAPLAN (by invitation), *Biochemical Research Lab., Massachusetts General Hospital, Boston*. The enzymatic condensation of acetate and sulfanilamide with adenylypyrophosphate as condensing agent is due to a dissociable coenzyme-enzyme system. The apoenzyme is prepared by autolysis or dialysis of pigeon liver extracts, dialyzed solutions also require an SH compound in addition to the coenzyme for activity.

The coenzyme is present in high concentration in liver, brain and pigeon breast muscle, some is found in kidney, spleen, pancreas and in red blood cells, little, if any, is present in rabbit muscle or yeast. So far the coenzyme has not been identified, wholly

or partially, with any known compound, coenzyme I and II, cocarboxylase, pyridoxal phosphate, folic acid conjugate and other substances were tried without effect. Complete decoloration by extraction with phenol excludes the possibility of a flavin derivative. The coenzyme-factor is destroyed by an enzyme present in liver extracts, by highly purified intestinal phosphatase, by relatively mild treatment with acid and alkali, by hydrogen peroxide. Its Hg, Pb and Ag salts are poorly soluble in acetic acid. The Ba salt is soluble in water and insoluble in 70 per cent alcohol. Purified preparations were obtained by fractionation of boiled pork liver extract. Our best preparations are 70 times more active per dry weight than the original boiled liver. We estimate that these preparations contain from 2 to 5 per cent pure compound. There are indications that the same coenzyme is concerned with (a) phosphorylation of acetate in pigeon liver and (b) with acetylation of choline in brain. [Supported by a grant from the Commonwealth Fund.]

Mechanism of the enzymatic synthesis of acetylcholine MORRIS A. LIPTON (introduced by E. S. Guzman Barron), Nachmansson and Machado¹ found that extracts from acetone dried preparations of brain can anaerobically synthesize acetylcholine (ACh) in the presence of adenosinetriphosphate (ATP), choline and certain substrates (glutamate, cysteine, citrate). It has been found that water clear extracts obtained after high speed centrifugation can also synthesize ACh. After dialysis no synthesis occurs unless the following are added: ATP, choline, potassium, certain thermostable substances (λ) present in boiled extracts of yeast, kidney or brain, and suitable acetyl donors (citrate, isocitrate, acetoacetate). Boiled extract cannot be substituted for by mixtures of Mn, Mg, diphosphothiamine, diphosphopyridine nucleotide, hexosediphosphate, and guanine. Acetate and glutamate have little activity as acetyl donors. Malonate and fluoroacetate do not inhibit the synthesis. Synthesis is increased on addition of semicarbazide with citrate as acetyl donor. In the presence of citrate equimolecular amounts of a keto acid (presumably oxaloacetic acid) and acetylcholine are formed. The following reactions presumably occur in these extracts:

- 1 Citrate \rightleftharpoons cisaconitate \rightleftharpoons isocitrate
 - 2 Isocitrate \rightleftharpoons oxaloacetate + acetate (active)
 - 3 Acetate (active) + choline + $\lambda \rightarrow$ acetylcholine
- With acetoacetate, reactions (1) and (2) are dispensed with. The reversibility of these reactions probably explains the inhibiting effect of α keto acids.

Lipotropic factors COLIN C. LUCAS (by invitation), C. H. BEST, JESSIE H. RIDOUT (by invitation).

¹ Nachmansson, D. and Machado, A. L. J. *Neurophysiol.* 6: 397 (1943).

tion) and JEAN M. PATTERSON (by invitation) *Banting and Best Dept of Medical Research, Univ of Toronto*. A re-investigation of the activities of the various lipotropic factors has been initiated. Quantitative data have been obtained by fractionation of the total liver lipids. The influence of the following factors is being systematically studied in the white rat: (a) the age of the animal, (b) the nature and amount of protein, the total labile methyl supply, and the organic sulphur content of the basal diet, (c) the presence of antilipotropic substances in the diet, (d) the food intake and (e) the possible synergistic effects of the various lipotropic agents. A series of titration curves illustrating the lipotropic effects of choline and inositol alone and in combination will be presented. Some preliminary observations on the influence of cholesterol, biotin, and a liver fraction upon these results will be reported.

Protein fractionation studies on the sera of control and injured dogs. STEPHAN LUDWIG, ERLAND C. GJESSING (by invitation) and ALFRED CHANUTIN. *Biochemical Lab., Univ of Virginia*. The proteins of the sera of dogs were fractionated by the alcohol procedures used at the Physical Chemistry Laboratories of the Harvard Medical School.

The serum of normal dogs is separated into 4 main fractions. The distribution of the proteins in dog serum is different from that observed in human serum treated by the same methods. Special procedures have been developed for subfractionating the fractions rich in alpha globulin.

The serum of dogs subcutaneously injected with turpentine has been fractionated into 6 main fractions. The 2 extra fractions are chiefly made up of alpha globulins. Fraction IV which contains most of the alpha globulin was subfractionated and yielded a number of fractions some of which were almost pure alpha globulin. One of these subfractions was water soluble and on analysis contained approximately 70 per cent of total lipid, which was chiefly cholesterol esters, free cholesterol and phospholipids. The per cent of free cholesterol was 33% of the total cholesterol. This material was precipitated from a salt-free aqueous solution by adjusting the pH to 5.8.

Other alpha globulin fractions, which were water soluble, contained smaller amounts of cholesterol and phospholipid.

All fractions have been characterized by electrophoretic mobilities, nitrogen, total lipid, free and ester cholesterol and phospholipid concentrations.

Composition of specific precipitates from anti-tobacco-mosaic-sera. SAUL MALKIEL (introduced by W. M. Stanley). *Rockefeller Inst for Medical Research, Princeton, N. J.* The quantitative behavior of viral-anti-viral systems has been but little investigated partly because of the lack of

purified and chemically characterized antigens. Tobacco mosaic virus, which is available in a highly purified form, is an extremely strong antigen. The anti sera prepared were of high titer for, at the point of optimal proportions, 0.007 cc of a given rabbit anti serum was found to be equivalent to 1 mg of tobacco mosaic virus when titrated by the method of Dean and Webb. The zone of optimal proportions did not coincide with the equivalence zone but was found to be in the region of excess antigen. Anti sera in the horse and rabbit were prepared and these systems studied. The quantitative relationships of the specific precipitates were established by a determination of the antibody and antigen content. Since this antigen contains a known amount of phosphorous the antigen content was estimated by means of phosphorous determinations. Electron micrographs prepared by the gold plating technique of complexes of known antibody-antigen composition were presented. In general, for the system studied, viral complexes were similar to those of lower molecular weight soluble proteins.

Metabolism of dehydroisoandrosterone. HAROLD L. MASON and EDWARD J. KEPLER (by invitation). *Dept of Biochemistry, Mayo Foundation, and Division of Medicine, Mayo Clinic, Rochester, Minnesota*. Our study of the metabolism of dehydroisoandrosterone has been continued by administration of dehydroisoandrosterone acetate to one woman (case 2) and one man (case 3) having Addison's disease. In our first study (J Biol Chem 160:255, 1945) the subject (case 1) was a man who had pituitary insufficiency. In this case unchanged dehydroisoandrosterone, androsterone, etiocholan-3(α)-ol-17-one and Δ^5 -androstene-3(α), 17(α)-diol were isolated from the urine. Similar results were obtained with cases 2 and 3 except that dehydroisoandrosterone could not be isolated in either case. Determination of the β alcoholic 17-ketosteroids in the ketonic fraction revealed none in case 2 and 13 per cent of the total in case 3. A trace of Δ^5 -androstene-3(α), 16, 17-triol was isolated in case 2 and also a nonketonic compound, $C_{19}H_{22}O_3$ (T), previously isolated from the urine of several cases of adrenal tumor (Mason and Kepler, J Biol Chem 161:235, 1945). In cases 1 and 3 almost twice as much androsterone as etiocholan-3(α)-ol-17-one was isolated, whereas in case 2 the amount of androsterone was only a fourth the amount of etiocholanolone. These results indicate that dehydroisoandrosterone is not an end product of steroid metabolism but can be almost completely transformed to unrecognized products and to androsterone and etiocholanolone, which are the chief ketonic steroids that have been isolated from normal urine. The results also suggest the possibility that dehydroisoandrosterone may be a primary product of the adrenal cortex from which, in

the females, the urinary androsterone and etiocholanolone are derived

An enzyme in the animal organism capable of hydrolyzing diisopropyl fluorophosphate ABRAHAM MAZUR *Biochemistry Section, Medical Division, Chemical Warfare Service, Edgewood Arsenal, Md* Extracts of rabbit, monkey and human liver, kidney and plasma were found to contain a factor capable of greatly accelerating the hydrolysis of diisopropyl fluorophosphate, to form F^- and diisopropyl phosphoric acid The hydrolysis products were unable to inhibit cholinesterase activity

It was shown that the liver plays a rôle in the *in vivo* destruction of diisopropyl fluorophosphate Eviscerated rabbits, whose livers were effectually removed from the general circulation, responded to injected diisopropyl fluorophosphate with a more marked lowering of the red cell and brain cholinesterase activities than did non eviscerated rabbits receiving the same dose of diisopropyl fluorophosphate

The factor present in liver, kidney and plasma was shown to be enzymic in nature, e g sensitive to moderately high temperatures and acid pH, non dialysable and inhibited by low concentrations of Hg^{++} , Cu^{++} and iodine The enzyme activity was proportional to its concentration in solution over a 20 fold range of dilution The enzyme from rabbit kidneys was concentrated 13 times on the basis of its nitrogen content Prolonged dialysis resulted in a partial loss of activity which could be restored almost completely by Ca^{++} or Mg^{++} Iodoacetate caused some inhibition but iodosobenzoate, F^- , Fe^{+++} , arsenite and cysteine did not inhibit the enzyme The enzyme activity is not related to phosphatase, cholinesterase or esterase activity

The fate of diisopropyl fluorophosphate in the animal organism is a resultant of the irreversible inactivation of plasma, red cell and tissue cholinesterases and the detoxification of the fluorophosphate, especially in the liver

Effects of acid beverages containing fluoride on the teeth and bones of dogs C M McCAY and (by invitation) J S RESTARSKI, J G BIERI, and ROSS A GORTNER, JR *Naval Medical Research Inst, Bethesda, Md* The effects of consuming 500 ml daily of a cola-type beverage (pH 2.6), with or without added fluorine, have been studied with six litter-mate puppies Two animals served as controls, one receiving water, the other sucrose solution, two were given a sucrose phosphoric acid (0.055 per cent) solution, the others received the sucrose acid solution containing 1 or 20 ppm fluorine (as NaF) As the deciduous teeth loosened they were extracted, the permanent teeth were studied when the dogs were sacrificed after 127 days

Both dogs receiving the acid beverage without fluorine showed sufficient etching of the enamel to

produce definite ridging at the gingival margin The effect was most prominent on the labial surfaces of the anterior teeth and lingual surfaces of the posteriors Generally, the lower teeth were more affected than the uppers

Sodium fluoride definitely reduced acid decalcification, but all teeth showed the high polish characteristic of mild acid attack The higher fluorine level (20 ppm) was more effective Areas of apparently abnormal bone porosity were noted on the mandible of the dog receiving 20 ppm F

Fluorine analyses of various tissues disclosed apparent differences only in the bones Whereas the two control dogs and those receiving the sucrose acid solution had bone fluorine levels of 132-148 ppm, those drinking solutions with 1 and 20 ppm fluorine had, respectively, bone levels of 192 and 298 ppm F The livers of all dogs contained 0.1-0.3 ppm F and the muscles contained 0.6-1.1 ppm F

Lysozyme as a Mucolytic Enzyme¹ KARL MEYER and ELEANOR HAHNEL (by invitation) *Dept of Ophthalmology, College of Physicians and Surgeons, Columbia Univ, and Institute of Ophthalmology, Presbyterian Hospital, New York* The mechanism by which lysozyme lyses susceptible microorganisms was explained as a hydrolysis or depolymerization of a substance of mucoid nature contained in the bacterial membrane² This substrate has now been isolated in its high polymer form

A rapid and accurate assay method for lysozyme activity has been developed, based on the depolymerization of the substrate as measured viscosimetrically In this method the viscosity of a solution (5 cc) containing 20 mg substrate is reduced to half by 0.7 gamma of pure lysozyme in 10 minutes at 37°C and pH 5.3 This reaction requires Cl^- , whereas the hydrolytic reaction measured by the increase in reducing power does not seem to require a halogen The same difference has been found with another mucolytic enzyme, hyaluronidase By this test tears contain 500 times more lysozyme than saliva

In the course of these studies lysozyme like enzymes were found in two plant proteases, papain and especially ficin A technical sample of ficin contained the equivalent of 25% of the crystalline lysozyme of eggwhite The plant lysozyme resembles the eggwhite and mammalian enzyme in that it lyses the same susceptible organisms, depolymerizes the mucopolysaccharides of these organisms, and hydrolyzes the glucosidic linkages, half of which can be measured as acetylhexosamine A partial separation from the proteolytic enzymes has been achieved by electrophoresis and chemical

¹ Supported by Josiah Macy Jr Foundation

² Meyer K, et al., *J Biol Chem* 113: 479 (1936)

methods The fecin enzyme is a less basic protein than eggwhite lysozyme

Effects of a single massive dose of vitamin D₂ on young dogs AGNES FAI MORGAN, HELEN E AXELROD (by invitation) and MARY GROOM (by invitation) *Lab of Home Economics, Univ of California, Berkeley* In an effort to examine further the effects of massive dose antirachitic practice, eight young dogs of two litters, 4 to 5 weeks old, were given a single dose of irradiated ergosterol, 314,000 to 530,000 I U vitamin D per Kg Within two weeks three were dead and a fourth was moribund in five weeks All exhibited the usual symptoms of overdosage, anorexia, polyuria, bloody diarrhea, excessive thirst and prostration

The three surviving dogs were observed for 211 days The serum Ca remained elevated for six months and Ca & P retention was marked On autopsy, extensive calcification of the lungs and moderate calcification in the hearts and kidneys was found in all the dogs, but the excess deposits were most striking in the dogs which succumbed or were sacrificed soon after the medication Some decalcification of the soft tissues took place during the recovery period in the three survivors The most striking abnormalities were found in the teeth and jaws Malocclusion, pitting, irregular placing and poor development were seen in all the dogs and these conditions were not appreciably improved during the eight months' recuperative period

Supplementation of casein and a casein hydrolysate with cystine and methionine ARTHUR J MUELLER (by invitation), WARREN M COX, JR and DOROTHY SLOAT (by invitation) *Mead Johnson & Company, Evansville* Twenty groups of 10 rats have been fed a purified diet containing 1.2% of nitrogen as the only source of protein Comparison of total gain in weight and gain in relation to nitrogen intake when casein, lactalbumin, and casein hydrolysate (Amigen) alone and after supplementation with various levels of methionine and cystine has been made Lactalbumin promoted greater gain in total weight and per gram nitrogen ingested than casein or Amigen, but the substitution of 1¼-2½% of methionine or cystine nitrogen for a portion of the total nitrogen gave results equal to those observed with lactalbumin Higher intake levels gave progressively poorer growth

When administered orally, subcutaneously and intravenously to dogs, the supplementation of Amigen with methionine resulted in improved nitrogen retention

Colorimetric method for the determination of lysine JOHN A NELSON (by invitation), WILLIAM D MCFARLANE and MARCEL BOULET (by invitation) *Dept of Chemistry, Faculty of Agriculture, McGill Univ, Quebec* A solution of brominated lysine develops a blue color when heated with phosphomolybdic-phosphotungstic acid This color

reaction, which will detect lysine at a concentration of 1 p p m, has been made the basis of a sensitive and rapid colorimetric method for the determination of lysine

Lysine and arginine are quantitatively separated from the other amino acids in a protein hydrolysate by adsorption on sodium decalco and the lysine content of the eluate is determined in the presence of arginine (which does not give the color reaction) by applying the color reaction after bromination

Satisfactory recoveries of added lysine have been obtained from mixtures of amino acids and from a gelatin hydrolysate The lysine content of several proteins has been determined and the results compared with those in the literature In general the values obtained by the colorimetric method are intermediate between those obtained by isolation procedures and those by microbiological methods

Enzymatic formation of C₄ tricarboxylic acids by CO₂ fixation SANTIAGO OCHOA *Dept of Chemistry, New York University College of Medicine, New York* It has previously been reported (Ochoa, J Biol Chem 159 213, 1945) that the formation of isocitric acid from α-ketoglutaric acid and CO₂ in the presence of oxalosuccinic carboxylase, manganese ions, isocitric dehydrogenase, and reduced triphosphopyridine nucleotide, can be increased by a coenzyme-linked dismutation with the glucose 6 phosphate dehydrogenase system of Warburg and Christian The isocitric acid formed in such a system has since been isolated as the barium salt and identified both by the action of isocitric dehydrogenase and by its conversion to citric acid by aconitase When the latter enzyme is also added to the above dismutation mixture the equilibrium is further shifted in favor of CO₂ fixation and large amounts of citric acid are formed Under these conditions the over-all reaction Glucose 6 phosphate + α-ketoglutarate + CO₂ = 6-phosphogluconate + citrate, has been followed by chemical estimation of the disappearance of both glucose 6-phosphate and α-ketoglutarate, and of the formation of citrate The reaction can also be followed manometrically through the liberation of CO₂ from bicarbonate by the phosphogluconic acid formed, since the disappearance of CO₂ by fixation is balanced by the formation of a carboxyl group of the tricarboxylic acid

I am indebted to Dr Erna Weisz-Tabori by her assistance in this work, and to Dr Erwin Haas for a generous supply of glucose-6-phosphate dehydrogenase [Aided by grants from the Rockefeller Foundation, The Penrose Fund of the American Philosophical Society, The Williams Waterman Fund of Research Corporation, and Hoffmann La Roche, Inc]

Storage of vitamin A as influenced by composition of the diet ELSA ORENT-KEILES and ELIZABETH C CALLISON (by invitation) *Bureau of*

Human Nutrition and Home Economics, U S D A Beltsville, Md As part of an investigation on the supplementary relationships among foods, a study was made of the vitamin A stores in the livers of animals receiving basal diets consisting of relatively large amounts of white or whole wheat bread together with cooked potatoes, kale, carrots, hydrogenated vegetable fat and sodium chloride. Vitamin D was provided in the form of viosterol. In parallel, modification of these two diets were fed in which part of the bread was replaced by oatmeal, navy beans, or skimmed milk, in amounts furnishing about the same quantity of protein.

The amount of carotene in the experimental diets furnished by the kale and carrots provided several times the minimal requirement of vitamin A for the rat as established by Goss and Gilbert (J Nutr 18 169, 1939).

Young piebald rats of known nutritional history from the same stock, weighing between 40-50 grams, were placed immediately after weaning (21-28 days of age) on the experimental diets which were fed *ad lib*. The animals were housed in individual cages without bedding and with raised bottoms of wire screen to prevent access to excreta. The livers of the mature rats fed these diets for over 200 days were analyzed for vitamin A content by the Carr-Price method, using the Evelyn photoelectric colorimeter.

The results showed that although the diets are similar in vitamin A value the liver reserves of vitamin A in these rats differed markedly with the composition of the diet. Studies are in progress to determine the factor or factors causing these differences.

A study of the composition of cardiolipin MARY C PANGBORN *Division of Labys and Research, New York State Dept of Health, Albany, N Y* When cardiolipin is saponified with KOH in absolute alcohol at room temperature, a precipitate (Fraction K-1) separates, this consists of water-soluble K salts and contains about 90 per cent of the total phosphorus. After the alcoholic soap solution is concentrated, diluted with H₂O, acidified, and extracted with petroleum ether for isolation of the fatty acids, the remaining 10 per cent of the phosphorus is found in the acid aqueous solution, largely as glycerophosphoric acid.

The fatty acids represent about 74 per cent of the original weight. No saturated acids are found. Hydrogenation yields stearic acid. The iodine number of 163 indicates a mixture of linoleic and oleic acids, no evidence of the presence of linoleic acid is obtained on bromination.

The precipitate K-1 yields two organic phosphoric acids, separable in the form of their Ba and Ca salts. The free acids are very easily hydrolyzed by diluted HCl or H₂SO₄, the only hydrolysis products so far identified are glycerol and glycerol

phosphoric acid. Cardiolipin is therefore a phosphatidic acid in which glycerophosphoric acid is replaced by a complex glyceryl-glycerophosphate ester.

The effect of CCl₄ poisoning on the fate of N'methylnicotinamide in the rat W A PERLZWEIG, J W HUFF (by invitation) and F ROSEN (by invitation) *Duke Univ Medical School, Durham*. It was previously shown (J Biol Chem, 150 401, 1943) that rat liver slices methylate nicotinamide to N'methylnicotinamide and that both man and rat "destroy" it further to unknown products (J Biol Chem, 161 417, 1945). In an attempt to study the rôle of the liver in this process, 100 mg of N'methylnicotinamide was administered orally to rats before and after acute poisoning with CCl₄ (0.25 ml subcutaneously for 2 days) and also 7 days later on recovery (as judged by food intake and gain in weight). The 48 hour excretion of F₂ in the urine of each rat is shown in the following table.

48 hour excretion of N methylnicotinamide

Rat	Control mg	2nd day of CCl ₄ mg	7 days later mg
1	32 1	46 6	33 1
2	29 7	42 3	23 4
3	21 6	37 1	22 5
4	25 2	36 9	28 1
5	30 3	43 9	30 1
Mean	27 7	41 4	27 4

It is apparent, therefore, that CCl₄ poisoning, diminishes the capacity of the animal to destroy N'methylnicotinamide. These results are surmised to be analogous to the increased excretion of N'methylnicotinamide after a test dose of nicotinamide observed in patients with liver disease.

Fate of sodium ricinoleate after oral administration to white rats ELIZABETH PINKERTON (by invitation) and E L MACQUIDDY (by invitation), *Univ of Nebraska, School of Medicine, Omaha*, and HARTMANN GOETZE (by invitation) and FRED W OBERST *Wm S Merrell Co, Cincinnati*. Little is known of the action of sodium ricinoleate in the intestinal tract when it is used in the treatment of certain chronic intestinal disorders. Studies were carried out in which sodium ricinoleate was either fed in a diet (approximately 0.5 grams per day for 2 months) or administered by stomach tube (400 mgm) to white rats, and the amounts absorbed from the gastro-intestinal tract or excreted in feces were determined. Animal charcoal was administered with the sodium ricinoleate by stomach tube to some of the animals to show the distance it had traveled down the intestinal tract at the time the animals were killed. The different groups of animals were killed 3, 6, 16, and 24 hrs, respectively, after the dose.

Fats and fatty acids were extracted from gastro-intestinal contents and feces, which subsequently were separated into petroleum ether (40-60°) and ethyl ether fractions. Acetyl numbers of the fatty acids of both fractions were determined.

There was no evidence that any ricinoleic acid was excreted in the feces of these animals when it was either fed with the diet or administered by stomach tube. Approximately 10% of a dose could be recovered from the gastro-intestinal tract 16 hrs after its administration by stomach tube. Sodium ricinoleate considerably retards the passage of animal charcoal down the intestinal tract.

Effect of adrenal cortex extract on the hexokinase reaction. WINSTON H. PRICE (by invitation), MILTON W. SLEIN (by invitation), SIDNEY P. COLOWICK and GERTY T. CORI. *Washington Univ. School of Medicine, St. Louis.* In muscle extracts from rats made diabetic with alloxan, the hexokinase reaction exhibits a latent period which is abolished by addition of insulin.¹ The latent period is apparently due to the preponderance of an inhibitory pituitary factor over insulin in such extracts, since a similar latent period, also released by added insulin, can be produced by addition of anterior pituitary extract to muscle extracts from normal rats.¹ This view is now supported by studies of the effect of adrenal cortex extract (Upjohn) on the hexokinase reaction in muscle extracts from normal and diabetic rats.

Cortical extract alone has no effect on hexokinase in normal extracts, but greatly intensifies the inhibitory effect of added or previously injected anterior pituitary extract. With extracts from diabetic rats, cortical extract alone often produces a marked and prolonged inhibition (30 to 80% inhibition by 0.05 cc of Upjohn extract in 2.5 cc of reaction mixture). This inhibition may be attributed to an intensification of the effect of a pituitary factor present in the diabetic muscle extracts.

Whenever inhibition by cortical extract is observed, insulin invariably releases the inhibition, about 50 γ of insulin being required to counteract the effect of 0.1 cc of Upjohn extract.

The adrenal factor appears to be one of the as yet unknown compounds in the amorphous fraction, since two different preparations² of the latter had a marked inhibitory effect, while crystalline compounds³ A, B, and E had no effect.

Variables affecting the precision of assay of estrogens. L. I. PUGSLEY. *Lab. of Hygiene, Dept. of National Health and Welfare, Ottawa, Canada.* The slope of the regression lines were calculated from the data obtained after subcutaneous and oral administration of a number of estrogens show-

ing that the subdivision of the doses, time of smearing and time of dosing were important factors in determining the precision of the biological assay of these substances.

Influence of decalcification on the determination of prothrombin. ARMAND J. QUICK. *Dept. of Biochemistry, Marquette Univ. School of Medicine, Milwaukee.* All known conditions of hypoprothrombinemia are due to a deficiency of component B of the prothrombin complex. A reduction of component A has not been observed in vivo. By increasing the relative concentration of component A in decalcified plasma, the prothrombin time can be definitely shortened (*Am. J. Physiol.* 140: 212, 1913) and this may be erroneously interpreted as hyperprothrombinemia.

In the present study, results have been obtained which indicate that component A is influenced by the decalcifying agent as well as by its concentration. When 9 volumes of blood are mixed with 1 volume of 0.1 M sodium oxalate, a plasma is obtained which has a prothrombin time that is the same as that of unaltered plasma mixed directly with thromboplastin. (For normal human plasma it is 12 seconds.) When human blood is mixed with 0.129 M sodium citrate in the ratio of 9 to 1, the plasma will have a prothrombin time of 10½ to 11 seconds, and on standing 24 hours this may decrease to 9 seconds. With higher concentrations of sodium citrate, a longer prothrombin time is obtained. The prothrombin time increases slowly in stored plasma when the low concentration of sodium citrate (0.128 M) is employed, whereas the decrease with a higher concentration (0.25 M) is much faster and is similar to that of oxalated plasma.

Apparently a close relationship exists between component A and calcium in the coagulation mechanism, and the present findings further emphasize the imperativeness of a rigidly standardized procedure for the quantitative determination of prothrombin.

Reaction of thiol compounds with hydrogen peroxide and peroxidase. LOWELL O. RANDALL. *The Wellcome Research Labs., Tuckahoe, N. Y.* Thiourea, thiouracil and other antithyroid compounds do not inhibit peroxidase but, on the contrary, are substrates for the hydrogen peroxide-peroxidase system. The apparent anti-peroxidase activities of thiol compounds, observed when using methods which depend upon the formation of a colored complex, are due to three factors: (1) the thiol compounds are reducing agents capable of preventing the formation of colored complexes or of reducing them after they are formed, (2) they reduce the hydrogen peroxide, thus removing it from the reacting system, (3) they act as competing substrates for the available peroxidase.

Hydrogen peroxide was determined in the War-

¹ *J. Biol. Chem.* 160: 633, 1945.

² Kindly supplied by Dr. Kendall and by Dr. Kuzenga.

³ Kindly supplied by Dr. Kendall.

burg apparatus by measuring the oxygen liberated from hydrogen peroxide by catalase. The activity of horse-radish peroxidase was measured manometrically by the rate of disappearance of hydrogen peroxide in the presence of various substrates. Some thiol compounds were found to be oxidized at measurable rates by hydrogen peroxide and the rates were accelerated by peroxidase. The oxidation of *p* aminobenzoic acid by the hydrogen peroxide-peroxidase system was inhibited by thiol compounds because they were competing substrates for the enzyme system. The thiol compounds did not inhibit peroxidase. These results were deduced from experiments applying the principles of Lineweaver and Burk (J Am Chem Soc 56 658, 1934).

The reducing power of the thiol compounds may be significantly related to their antithyroid properties.

Synthesis of cholesterol in liver slices D RITZENBERG, ERNEST BOREK (by invitation), and KONRAD BLOCH *Dept of Biochemistry of the College of Physicians and Surgeons and the New York State Psychiatric Inst and Hospital, New York*. Previous studies have shown that liver slices utilize the carbon atoms of acetic acid for the synthesis of cholesterol. With this technique synthesis of cholesterol can be demonstrated in liver, but not in kidney, spleen, testes, heart or intestine. These results suggest that the liver is the chief site of biological cholesterol synthesis. In the intact animal deuterio alanine acts as a source of acetyl group for the acetylation of phenylaminobutyric acid but does not give rise to deuterio cholesterol. In accordance with this finding, liver slices do not utilize alanine for the synthesis of cholesterol. The same is presumably true for pyruvic acid, which under these conditions is readily formed from alanine. Incubation of liver slices with deuterio ethanol (CHD CH OH) yields cholesterol with high concentrations of deuterium. The rôle of acetic acid, ethanol and acetaldehyde in the mechanism of the synthesis of cholesterol will be discussed.

Distribution of ascorbic acid in blood JOSEPH H ROE, CARL A KUETHER, and RUTH G ZIMLER (by invitation) *School of Medicine, George Washington Univ, Washington, D C*. The ascorbic acid content of the whole blood and the plasma has been determined in 52 guinea pigs, in 50 healthy fasting human subjects, and in 50 hospitalized fasting patients. In the guinea pigs and the healthy human subjects the ratio of the level of ascorbic acid in the plasma to that in the whole blood followed a characteristic pattern. At whole blood levels below 0.6 mg per 100 ml the plasma concentration was observed to be lower than the whole blood concentration, at whole blood levels of 0.6 to 0.9 mg per 100 ml the plasma content was found to be equal to, or slightly higher or lower than, the whole blood

content, the variations being about the same in each direction, at whole blood levels above 0.9 mg per 100 ml the plasma concentration was consistently higher than the whole blood concentration. In the patients the plasma level was lower than the whole blood level in all cases. These data appear to show (1) plasma ascorbic acid is more labile than whole ascorbic blood acid, (2) in healthy subjects with whole blood levels of ascorbic acid below 0.6 mg per 100 ml there is a negative balance between intake and bodily needs for ascorbic acid, (3) an adequate whole blood level of ascorbic acid is a value above approximately 0.6 mg per 100 ml and an adequate intake of ascorbic acid for healthy subjects would be an amount that will maintain the whole blood level above this concentration.

Concentration and properties of a chick growth factor occurring in cow manure MAX RUBIN and H R BIRD (introduced by N R Ellis) *Agricultural Research Center, Beltsville, Md*. Evidence has been obtained to show that there is a new unidentified factor present in cow manure, which stimulates the growth of chicks fed a diet of yellow corn, soybean meal, alfalfa meal and mineral and vitamin supplements. The factor is not identical with the L casei factors (from liver, yeast or fermentation residues), factors U, R, S, vitamins B_{10} or B_{11} , synthetic folic acid (Lederle), or pyracin lactone.

A method has been devised for extracting the growth substance from cow manure and a procedure developed for concentrating it. Optimum growth has been obtained by feeding as little as 4-7 mg of the concentrate per 100 grams of diet. The growth factor as it is present in cow manure is moderately soluble in water, 50% ethyl alcohol and 95% ethyl alcohol, it is insoluble in chloroform and ether. The factor after extraction is stable to heat in the dry state at 100°C for 1 hour and autoclaving in solution for 15 minutes. It will not dialyze through cellophane and is precipitated from solution at pH 3.0.

The factor can be transmitted from the hen through the egg to the chick.

Effects of chronic intoxication of rats with DDT on lipids and other constituents of liver HERBERT P SARETT and BERNARD J JANDORF (introduced by Oscar Bodansky) *Chemical Warfare Service, Edgewood Arsenal, Md*. Adult rats (13) which received 50 mg of DDT per kg in oil daily for 30 to 100 days showed a statistically significant increase in the concentration of liver lipids (19.2 per cent of liver dry weight) when compared to 14 controls which received equivalent amounts of the oil alone (14.7 per cent). Further studies with 150-180 grams rats receiving 0.07 per cent DDT (Group B) or 0.07 per cent DDT and 0.2 per cent choline hydrochloride (Group C) incorporated into a ground stock diet and fed ad lib for 36 to 40 days, showed similar changes. During the experimental

period 2 of the 16 rats in group B and 6 of the 16 in group C died. No mortality occurred in the 12 rats of control group (A). The livers of rats that received DDT weighed about 40 per cent more than those of group A. The per cent of water and of glycogen was the same for all three groups. The total lipids comprised 11.8 per cent of the dry weight of the livers of group A, compared to 18.5 and 18.4 per cent for groups B and C, respectively. The proportion of phospholipids (measured by phosphorus content) to total lipids was the same in all of the groups, while the proportion of total cholesterol to total lipids was significantly decreased in groups B and C. The increased weight of the livers of groups B and C was associated with an overall increase of about 75 per cent in the weight of total lipids per liver, a similar increase in phospholipid phosphorus content and a smaller increase in total cholesterol.

Glutamic acid decarboxylase of higher plants
 OTTO SCHALES, VIRGINIA MIMS (by invitation) and SEIMA S. SCHALLER (by invitation) *Chemical Research Lab., Alton Ochsner Medical Foundation, New Orleans*. OKUNUKI (Bot. Mag. Tokyo 51: 270, 1937) discovered in higher plants an enzyme which specifically decarboxylated glutamic acid. He described glutamic acid decarboxylase as bound to the cellular structures from which it could not be brought into solution by treatment with glycerol, phosphate buffers and NaCl solution.

We obtained clear solutions of glutamic acid decarboxylase by mixing plant material for 3 minutes in a Waring Blendor with one to five volumes of ice cold phosphate buffer (pH 6.4), followed by storage in a refrigerator for one hour and subsequent removal of undissolved particles. The percentage of the total activity appearing in the solutions depended on the freshness of the plant tissues. Fresh carrots for example released into five volumes buffer only 25 per cent of the total activity, whereas 70 per cent were found to be soluble after 4 days storage of the carrots in a refrigerator. This is interpreted as a result of autolytic processes occurring during storage.

Clear solutions of glutamic acid decarboxylase lost part of their activity on dialysis. The original activity was restored or surpassed on addition of pyridoxal phosphate. The enzyme is apparently a pyridoxal-phosphate-protein complex. The first step in the reaction with glutamic acid seems to be a condensation between the aldehyde group of pyridoxal and the amino group of the acid. HCN and various aldehyde reagents by reacting with the aldehyde group prevent this condensation and therefore inhibit enzymatic activity.

Microdetermination of sphingomyelin in tissues
 G. SCHMIDT, J. BENOTTI (by invitation) and S. J. THANNHAUSER *Boston Dispensary, J. Pratt Diagnostic Hospital, and Tufts Medical School,*

Boston. The method is based on the observation that lecithin, hydrolecithin and all cephalins are quantitatively transformed into acid soluble P compounds during incubation with aqueous N potassium hydroxide for 15 hours at 37°. Under these conditions the P-containing group of sphingomyelin remains insoluble in acids.

The resistance of sphingomyelin against alkali under these conditions was substantiated on pure sphingomyelin which was isolated from lung by a new procedure developed by Thannhauser and Benotti. The resistance of brain sphingomyelin could be demonstrated by the absence of sphingosine in the acid soluble P compounds obtained from brain protagon after alkali treatment.

For the actual determination the tissues are extracted according to Bloor with a boiling mixture of alcohol and ether and subsequently with boiling mixture of chloroform and methanol. The combined extracts are concentrated to dryness under reduced pressure and the lipids are redissolved in petroleum ether containing approximately 10 per cent ethanol. An aliquot of the petroleum ether extract serves for the determination of the total lipid P. A second aliquot is evaporated to dryness. The lipids are finely suspended in aqueous N KOH and incubated at 37° for 15 hours. After acidification with a mixture of dilute hydrochloric and trichloroacetic acids, the amount of total P in the clear filtrate is determined. The P content of the filtrate represents the monophosphatide P, the difference between the total lipid P and monophosphatide P that of the sphingomyelin P.

Oxidation of 1,3,4-dihydroxyphenylalanine by normal and scorbutic kidney tissue
 ROBERT R. SFALOCK and TIEN HO LAN (by invitation) *Chemistry Dept., Iowa State College, and Dept. of Vital Economics, Univ. of Rochester*. The feeding of 1,3,4-dihydroxyphenylalanine has previously been found to increase the ascorbic acid requirement of the guinea pig. In further investigation of this relationship, the oxygen consumption and carbon dioxide production of normal and scorbutic kidney and liver slices of guinea pigs has been determined with the amino acid as the substrate. Of the two tissues, the kidney exhibits the more marked ability to oxidize the substrate. In the presence of the amino acid, the Q_{O_2} is increased by 50% and the Q_{CO_2} by 40%. When kidney slices from scorbutic animals are used the Q_{O_2} and Q_{CO_2} values of the control and experimental flasks are identical. The difference between the normal and scorbutic state is further emphasized by the ratio of excess oxygen to amino acid present (normal—1.4 atoms per mol, scorbutic—0). With the administration of crystalline ascorbic acid to the scorbutic animal for six days prior to use, the kidney slices regain their ability to oxidize dihydroxyphenylalanine. These results afford additional evidence that

metabolism of this compound is dependent upon an adequate intake of ascorbic acid

Changes in the serum proteins and carbohydrate in tuberculosis and methods of analysis F B SEIBERT, JANE ATNO and MABEL V SEIBERT (by invitation) *Henry Phipps Institute, Univ of Pennsylvania, Philadelphia* The proteins were determined by means of electrophoresis using veronal buffer pH 8.5 and $\mu = 0.1$ The polysaccharide was determined by means of the carbazole reaction of Dische adapted for use with the photoelectric colorimeter An indirect method based upon the difference between total carbohydrate so determined and glucose measured by means of the Somogyi iodometric titration, gave the same results as a direct method in which the true polysaccharide was determined upon an alcohol precipitate of the serum The reliability of the method was established The proper standard was determined by choosing the pure sugar or combination of sugars which after reacting with carbazole gave an absorption curve similar to that given by serum The limitations of the method will be discussed

No significant change occurs over long periods of time in the glucose or true polysaccharide content of serum if it is kept frozen or at the point of freezing

Analyses on sera from normal and tuberculous patients in different stages of the disease showed a progressive increase in polysaccharide content and a corresponding decrease in albumin/globulin ratio with advancement of the disease There was an actual decrease in albumin and an increase in the gamma and alpha globulin concentrations

The concentration of polysaccharide in normal serum is approximately 99 mgms per cent and may increase one hundred per cent or more in cases of far advanced tuberculosis

Relatively insignificant changes occur in the same individual from time to time or are caused by ingestion of carbohydrates

Replacement of vitamin A₁ by Vitamin A₂ in the retina of the rat E M SHANTZ (by invitation), N D EMBREE (by invitation), H C HODGE and J H WILLS, JR (by invitation) *Univ of Rochester, Rochester, N Y* Vision in dim light is due to the photochemical decomposition of 'visual purple' or rhodopsin, a retinal pigment having an absorption maximum at 500 m μ Certain freshwater fish possess a visual purple system differing from that found in most animals This pigment, called porphyropsin, has an absorption maximum at about 522 m μ Rhodopsin is believed to be a conjugated protein in which vitamin A₁ is a prosthetic group, while the prosthetic group in porphyropsin is believed to be vitamin A- It was the purpose of this experiment to determine whether an animal normally utilizing only vitamin A₁ in its retinal pigment could develop porphyropsin through the

replacement of vitamin A₁ by vitamin A₂ in the diet

The visual purple extracts from three large groups of albino rats were examined in a recording spectrophotometer The first group, which were normal rats on a well-balanced diet, showed a good rhodopsin curve with a maximum at 500 m μ The second group, which had been on a vitamin A-deficient diet for a period of 9 weeks, also exhibited a rhodopsin curve but possessed only about $\frac{1}{4}$ the amount of pigment found in the normal retinas The third group, which had been administered a daily supplement of vitamin A₂ for 12 weeks after previous depletion, showed normal amounts of visual purple but the absorption maximum had been shifted to 520 m μ

Observations were also made on the effect of vitamin A₂ administration on the vitamin A picture in the liver and the blood stream A possible sex difference in utilization of this vitamin is also discussed

Studies on the formation of heme and on the average life time of the human red blood cell DAVID SHEMIN and D RITTENBERG *Dept of Biochemistry, Columbia Univ, New York* The feeding of glycine labeled with N¹⁵, to a human resulted in the formation of heme containing a high concentration of N¹⁵ From quantitative considerations it was concluded that glycine is the nitrogenous precursor of the protoporphyrin of hemoglobin We have also studied the formation of heme in the rat by feeding glycine, *dl* proline, *dl* glutamic acid, *dl* leucine and ammonium citrate labeled with N¹⁵ Since the isotope concentration of the labeled substances fed were not all the same, we have calculated the isotope concentration of the isolated heme on the basis that the fed material contained 100 per cent N¹⁵ On this basis the isotope concentration of the heme was 0.91, 0.25, 0.17, 0.16, and 0.09 after the feeding of glycine, *dl* proline, *dl* glutamic acid, *dl*-leucine, and ammonium citrate respectively The data show that of the compounds studied only glycine is directly utilized for heme formation The N¹⁵ concentration found in heme after the feeding of compounds other than glycine is a reflection of the utilization of their nitrogen for glycine synthesis

We have followed the isotope concentration of heme in human red blood cells for several months after the feeding of glycine labeled with N¹⁵ From the shape of the curve *vs* time, it is concluded that the average life time of the human red blood cell is about 125 days and that the porphyrin moiety of hemoglobin is not reutilized for hemoglobin formation

Lipid-mustard compounds R G SINCLAIR, G HALE, and D FAIRBAIRN (by invitation) *Dept of Biochemistry, Queen's Univ, Kingston, Canada* Aqueous sols of the cephalins and lecithins react

with dichlorodiethylsulphide (mustard) with the formation of compounds, some of which possess radically different properties from those of the original lipids

In the case of the cephalins, at least two and probably three groups are involved in the reaction, one is certainly the amino group. When the pH during the reaction is kept between 3.5 and 4.5, reaction with the amino group is practically excluded, the resultant compounds contain about 1 per cent or 3 per cent S, depending upon the particular cephalin used. Since one outstanding difference between the cephalins used is in the serine content, it seems likely that the carboxy group is involved in the reaction. When the pH during the reaction is increased, there is a progressive decrease in the free amino N and an increase in the S contents of the resultant product. At a pH of 9 the product may contain no free amino N and contains about 6 per cent S.

Lecithins (brain and egg), prepared through the CdCl_2 double salt, reacted with mustard to form compounds containing 1.7 to 2.3 per cent S. It is thought likely that the phosphoric acid group of the lecithins, and of the cephalins as well, is involved in the reaction.

The hydrophilic property of the mustard-cephalin compounds seems to be primarily a function of the free amino N content, those with only about $\frac{1}{3}$ of their amino groups free can not be dispersed in water.

Effect of tryptophane on urinary excretion of nicotinic acid in rats S. A. SINGAL (by invitation), A. P. BRIGGS, V. P. SIDENSTRICKER and JULIA LITTLEJOHN (by invitation) *Univ. of Georgia School of Medicine, Augusta*. Rats, when placed upon the low protein, high corn grits diet of Krehl et al.¹, showed a sharp decrease in urinary nicotinic acid as assayed microbiologically with *Lactobacillus arabinosus*. The addition of 1.0 mg per cent nicotinic acid or the increase of the casein content of the diet to 20 per cent did not alter the amount of nicotinic acid excreted. When 0.5 per cent l(-) tryptophane was included in the diet, a large increase was observed in urinary nicotinic acid, which upon acid hydrolysis, but not alkaline hydrolysis, was increased further some two to three fold. Lloyd's reagent and charcoal adsorbed in excess of 90 per cent of the urinary nicotinic acid, whereas, zinc hydroxide was ineffective in this respect. The study of the fecal excretion of nicotinic acid in these animals did not yield results which could be correlated with urinary data.

Tryptophane, when administered to rats maintained on commercial animal food, caused a three fold increase in the excretion of nicotinic acid in

the urine, which upon acid hydrolysis showed a further fifteen fold increase. Essentially similar results were observed when these urines were analyzed chemically for nicotinic acid, employing the cyanogen bromide and metol reaction.

Results of human studies will also be reported [*Acknowledgment, is made of aid from the John and Mary Marlic Foundation*].

Immune proteins of the cow EMIL L. SMITH (introduced by O. Wintersteiner) *E. R. Squibb & Sons, New Brunswick, N. J.* Immunity may be passively transferred from mother to offspring via the milk. The immune globulin of bovine milk and colostrum has now been isolated in electrophoretically homogeneous state. This globulin is easily differentiated from the well-known β lactoglobulin which possesses no immune properties. The immune protein has its isoelectric point at pH 5.9-6.1 and its diffusion constant ($D_{w, 20^\circ}$) is 3.6×10^{-7} sq cm per sec. On dialysis the immune protein separates into pseudo- and euglobulins, both of which possess immune activity. Analysis of the total immune globulin gave the following preliminary values (in per cent): hexose = 2.7, hexosamine = 1.5, total N (Dumas) = 15.5, total S = 1.04, tryptophane = 2.5, phenylalanine = 3.7, valine = 8.6 and leucine = 9.4.

In the plasma of the cow, the immune activity is present in both T and γ components similar to those found in the horse. Both of these components have been isolated and characterized. For the T component, the IEP is at pH 5.9-6.1, and for the γ , the IEP is at pH 7.0-7.2. The diffusion constants of both are similar to those of the milk and colostrum, indicating that all of these immune proteins are of approximately the same size. The analytical composition of the plasma proteins has been compared with those of the milk and colostrum. The results indicate that these proteins are closely related but not identical. Anaphylactic tests with guinea-pigs gave strong cross reactions between all of these proteins.

Metabolism of large doses of para-aminobenzoic acid PAUL K. SMITH, and (by invitation) JANE R. BAYLISS, S. ORGOZALEK and MARGARET M. McCLEURE *AAF School of Aviation Medicine, Randolph Field, Texas*. Methods were devised for determining in the urine the free and conjugated forms of p-aminobenzoic acid and of p-aminohippuric acid. These were based on the usual diazo reaction employed for sulfonamides plus the observation that ethylene dichloride would extract much of the free p-aminobenzoic acid and very little of the free p-aminohippuric acid from buffered dilutions of the urine.

After four gram oral doses, the plasma levels of p-aminobenzoic acid rose sharply and were maximal in about one hour and then fell rapidly. The proportion of the free form in the plasma varied

¹ Krehl, W. A., Teply, L. J., Sarma, P. S., and Elvehjem, C. A., Science 101: 489, 1945.

from 20 to 100 per cent, the proportion in the urine of the four fractions was likewise variable but in general most of it occurred as free p aminobenzoic acid or conjugated p-aminohippuric acid with smaller quantities of conjugated p aminobenzoic acid or free p aminohippuric acid

Estimation of vitamin A in fish liver oils by activated glycerol dichlorohydrin ALBERT E SOBEL and HAROLD WERBIN (by invitation) *Pediatric Research Laby, Jewish Hospital, Brooklyn* A comparative study was made of the vitamin A values obtained on the whole and on the unsaponifiable fractions of fish liver oils by activated glycerol dichlorohydrin, the Carr Price reaction, and the $E_{1\text{cm}}^{1\%}$ 328 $m\mu$ The procedures employed were those previously presented by the authors (*J Biol Chem*, 159 681, 1945)

On the whole oils, the values obtained by the antimony trichloride method were about 4% higher and the $E_{1\text{cm}}^{1\%}$ 328 $m\mu$, about 33% higher than those obtained with activated glycerol dichlorohydrin

On the unsaponifiable fraction of the fish liver oils, the antimony trichloride values were about 3% lower than the activated glycerol dichlorohydrin values, while the $E_{1\text{cm}}^{1\%}$ 325 $m\mu$, values were about 23% higher

Thus the new reagent approximates the values given by antimony trichloride with vitamin A in fish liver oils Since activated glycerol dichlorohydrin is stable over a period of two to three months, is not affected by traces of moisture, and gives a color with vitamin A which is stable for at least 8 minutes, it offers definite advantages over the antimony trichloride in the estimation of vitamin A in fish liver oils [This study was aided by a fund granted by the American Home Products, Corp and by a grant from the United Hospital Fund of the City of Greater New York]

Activated glycerol dichlorohydrin, a new colorimetric reagent for vitamin A ALBERT E SOBEL and HAROLD WERBIN (by invitation) *Pediatric Research Laby, Jewish Hospital, Brooklyn, N Y* Glycerol dichlorohydrin from various firms could not be relied upon to possess chromogenic power toward vitamin A (*J Biol Chem*, 159 681, 1945) However, the addition of various reagents such as acetyl chloride, anhydrous aluminum chloride, and benzoyl chloride produced a reagent with chromogenic power Acetylated glycerol dichlorohydrin was found to be inactive both toward vitamin A and vitamin D even with activating agents added

The best method of activating glycerol dichlorohydrin toward vitamin A was distillation under vacuum with 1 to 5% of antimony trichloride The activated reagent was found to be stable over a period of two to three months Under these conditions used for vitamin A determinations the inter-

ference of vitamin D and other related sterols is negligible

The absorption spectrum was taken on the Beckman spectrophotometer between 320 to 750 $m\mu$ of the violet color produced by reacting the reagent with crystalline vitamin A alcohol, crystalline vitamin A acetate, a natural vitamin A ester concentrate and its unsaponifiable fraction In each case one maximum was observed between 553 and 556 $m\mu$ The extinction $E_{1\text{cm}}^{1\%}$ of the vitamin A in the natural ester concentrate and its unsaponifiable fraction were almost identical, 1420 and 1410, respectively The color is stable from 2 to 10 minutes after addition of reagent A nearly linear relationship was observed at 555 $m\mu$ between 1.26 and 13.63 μg of vitamin A in 5 ml of reaction mixture [This study was aided by a fund granted by the American Home Products, Corp and by a grant from the United Hospital Fund of the City of Greater New York]

The hydrolysis of sphingomyelin WARREN M SPERRY and FLORENCE C BRAND (by invitation) *Dept of Biochemistry, New York State Psychiatric Inst and Hospital, New York* In applying the micro method reported last year (*Fed Proc*, 4 104, 1945) to the determination of choline in lipids it was desirable to employ a volatile acid as hydrolytic agent, so the hydrolysis, precipitation, filtration, and oxidation of choline reneckate could be carried out in the same tube Methanolic HCl yielded erratic results, but ethanolic HCl was found to be a satisfactory hydrolytic agent for the determination of choline in lecithin However, choline was split off from sphingomyelin only to a small degree even after long heating with strong ethanolic or aqueous HCl solutions Constant boiling HI liberates choline from sphingomyelin quite rapidly, hydrolysis appears to be complete within 3 hours at 137° in sealed tubes Heating with HI renders choline partially insoluble in cold secondary butanol, but in boiling butanol it usually dissolves with liberation of iodine This result is best explained by the assumption that a periodide is formed, but occasional somewhat low recoveries (down to about 90 per cent) after heating choline with HI suggest that a more deep seated change may occur We have some evidence that considerably more choline is yielded by hydrolysis of sphingomyelin with HI than with $\text{Ba}(\text{OH})_2$

X-ray diffraction studies on gallstones M SPIEGEL ADOLF and G C HENRY (by invitation) *Depts of Colloid Chemistry and Physics, Temple Univ School of Medicine, Philadelphia* The chief constituents of gallstones as well as their structures may be investigated by x-ray diffraction Nevertheless only a few pertaining studies are available We have tried diffraction studies of the stones both with powder and with thin sections

Powdered gallstones also were fractionated by treatment with various extracting fluids and diffraction pictures of the individual fractions were made. Cholesterol stones forming a group which showed multiple facettes and apparently concentric layers gave the following findings. Material scraped either from the surface or else from the center of a stone produced identically the same powder diffraction pattern as that of pure cholesterol. A section perpendicular to the surface gave a well-oriented picture indicating that crystallization occurred under stress within the stone. Another group of multiple dark brown stones showed the same powder diffraction pattern both in samples scraped from the surface and from the center. Sections cut at right angles to each other did not show signs of orientation. Both of these patterns seem to consist of at least two groups of substances. One group was identified as cholesterol, containing perhaps small ergosterol admixtures. Contrary to Ranganathan (Ind J Med Res 19:1153, 1932) no contraction of the cholesterol rings in the gallstone could be observed, the patterns remaining unchanged after extraction. The powder diffraction pattern of the substance remaining after the extraction of cholesterol indicates the presence of a mixture of $\text{Ca}(\text{H}_2\text{PO}_4)_2$ and $\text{Ca}_3(\text{PO}_4)_2 \cdot 12\text{H}_2\text{O}$ with a prevalence of the former constituent.

Enzymatic action of cerebrospinal fluids following concussion. M. SPIEGEL-ADOLF, H. T. WICIS (by invitation) and E. A. SPIEGEL (by invitation). *Depts. of Colloid Chemistry and Exp. Neurology, Temple Medical School, Philadelphia.* Our spectrophotometrical findings in the CSF (Fed Proc 4:105, 1945) in cerebral concussion were confirmed on a larger material. However, if the CSF was kept standing, its selective absorption band with its peak at $265 \text{ m}\mu$ became weaker and finally disappeared, although the sample was kept under sterile conditions. Temperature seems to have a marked effect on the velocity of this reaction. In order to analyze it, samples of commercial nucleic acids of animal (Difco) and of plant origin (Schwarz) were mixed with CSFs from patients who had recently sustained a concussion. Controls were set up both with normal human CSF and with saline solution. After an incubation of 4 hours at a temperature of 37° , spectrophotometrical measurements were made with a Hilger spectrophotometer as well as with a Beckman photoelectric quartz spectrophotometer. Both nucleic acid samples incubated with the CSFs from concussed patients showed a decrease of the selective absorption, while the controls remained unchanged. The changes produced in plant nucleic acids seem to exceed the ones observed in the animal nucleic acids. An effect upon animal nucleic acids could also be detected by a decrease of the Dische diphenylamine reaction. This may serve as base for a colorimetric

reaction characteristic of changes occurring in the CSF following concussion. This behavior of CSF of concussed patients can be explained by the presence of enzymes and may be related to the chromatolytic changes induced by cerebral concussion [Aided by a grant from the John and Mary R. Marille Foundation].

The chemistry and biological significance of hydroxyketo acids. DAVID B. SPRINSON and ERWIN CHARGAFF, *Dept. of Biochemistry, Columbia Univ., New York.* The breakdown of serine by several biological systems was previously shown to proceed by way of a dehydration to pyruvic acid and ammonia (L. Chargaff and D. B. Sprinson, J. Biol. Chem., 151:273, 1943). In contrast to this mechanism, rat kidney slices in bicarbonate buffer have been found to produce hydroxypyruvic acid, $\text{HOCH}_2\text{COCOOH}$, and ammonia. Following the deamination of *dl* serine in the presence of arsenite, hydroxypyruvic acid 2,4-dinitrophenylhydrazone was isolated and 22 per cent of the theoretically possible ammonia were recovered, 65 per cent of the amino acid remained unattacked. A similar experiment with *l* serine gave no hydrazone and almost 90 per cent of the amino acid were found intact. No hydrazone was obtained from *dl*-threonine.

Synthesis of β -hydroxy- α -keto acids was achieved by the careful hydrolysis of the corresponding β -bromo α -keto acids. Bromopyruvic and β -bromo α -ketobutyric acids yielded solutions of hydroxypyruvic and β -hydroxy- α -ketobutyric acids respectively. Both acids gave crystalline 2,4-dinitrophenylhydrazones, that of the hydroxypyruvic acid being identical with the derivative obtained by the deamination of *dl*-serine by rat kidney.

The structure of the synthetic hydroxypyruvic acid was proved through its cleavage by periodic acid to formaldehyde and oxalic acid and by the reduction of its dinitrophenylhydrazone to *dl* serine. Similarly, periodic acid produced acetaldehyde and oxalic acid from hydroxyketobutyric acid.

Hydroxypyruvate in 0.8 N alkali quickly formed the enediol, dihydroxyacrylic acid. Exposure to 0.01 N alkali produced a rapid and complex series of tautomeric changes and condensations accompanied by an increased periodate consumption.

Studies on thymus nucleohistone. KURT G. STERN and SANFORD DAVIS (by invitation). *Dept. of Chemistry, Polytechnic Inst., Brooklyn, N. Y.* Continued experiments on desoxyribonucleoproteins in 1 M NaCl solutions (Fed Proc 4:105, 106, 1945) have led to the conclusion that calf thymus nucleohistone is largely split into sodium thymonucleate and histone chloride. The sharp boundary (S at infinite dilution, approx. 30), previously observed in these solutions in the analytical ultracentrifuge, is likely that of the

nucleic acid component rather than of the nucleoprotein, since added thymonucleate fails to give an additional boundary

Ultracentrifugal analysis of water extracts of thymus tissue washed with 0.9 per cent NaCl reveals sedimentation of two major and one minor component. Nucleohistone isolated from water extracts by precipitation at 0.14 M NaCl shows a principal component and small amounts of lighter impurities. Both crude and purified solutions are unstable and no longer yield precipitates at 0.14 M NaCl after aging.

Extraction of thymus with 1 M glycine affords protein solutions of increased stability. In the ultracentrifuge, two major components and one minor component as well as a large concentration gradient at the meniscus were observed. At 0.14 M NaCl a nucleoprotein precipitates; its solution in 0.02 N phosphate, pH 7, shows only one sedimenting boundary while in M glycine an additional gradient develops at the meniscus. Glycine as a solvent for extracting nucleoproteins from tissues appears preferable to M NaCl; the low viscosity and absence of flow birefringence in glycine solutions indicate that the nucleoprotein is not dissociated in this solvent. *Histone*, prepared from thymus according to Felix, separates in the ultracentrifuge into a light and heavy fraction of similar arginine content. [This work was aided by the Carrie S. Scheuer Foundation.]

Effect of insulin level upon lipogenesis. DEWITT STETTEN, JR., and BABETTE V. KLEIN (by invitation) *Dept. of Biochemistry, College of Physicians and Surgeons, Columbia Univ., New York.* When fatty acids are synthesized in the liver of an animal whose body fluids contain D₂O, deuterium appears stably bound in the fatty acids. Advantage has been taken of this fact to evaluate the effect of hypo- and hyperinsulinism upon the rate of lipogenesis. Previously, in the rat,¹ and now in the rabbit it could be shown that in alloxan diabetes fatty acid synthesis proceeds at a rate well below normal. The converse effect, increased lipogenesis in the liver of the normal rabbit in response to administered insulin, has now been demonstrated. The deuterium concentration in the liver fatty acids of the rabbit has been elevated to four times the level of the control by the repeated injection of insulin. From this it has been concluded that the rate of utilization of glucose in hepatic lipogenesis is dependent upon the level of circulating insulin and represents a special case of the more general effect of insulin upon utilization of glucose. [Aided by grants from the Josiah Macy, Jr., Foundation and the Nutrition Foundation, Inc.]

d-Amino acid oxidase of *Proteus morganii*. P. K. STUMPF (by invitation) and D. E. GREEN *Depts.*

of Medicine and Biochemistry, College of Physicians and Surgeons, Columbia Univ., New York. We have previously described¹ the preparation of an enzyme from *Proteus vulgaris* which catalyzes the oxidation of *l* amino acids by molecular oxygen. Extracts from the same organism and *Proteus morganii* are now found to contain another enzyme which catalyzes the oxidation of *d* amino acids. This enzyme was extracted following disintegration in the Booth Green bacterial crushing mill or by ultrasonic irradiation. The enzyme which is associated with insoluble particles can be concentrated by isoelectric precipitation or by precipitation with ammonium sulfate. The enzyme oxidizes the *d* isomers of alanine, phenylalanine, phenylamino-butyric acid, histidine, methionine, and glutamic acid in the descending order of velocities named. *d*-Leucine and *d*-valine are very slowly if at all oxidized. *l*-Alanine and β -alanine are not oxidized. For each mole of amino acid oxidized one atom of oxygen is taken up and one mole of keto acid and ammonia are formed. There is no evidence of hydrogen peroxide formation by the bacterial enzyme in contrast to its formation by the *d*-amino acid oxidase of animal tissues.

The *d* amino acid oxidase of animal tissues is a flavoprotein. However the available evidence suggests that the *d*-enzyme of *Proteus* is not a flavoprotein. On dialysis the *Proteus* enzyme loses activity which can be restored by boiled extracts of yeast but not by flavin dinucleotide. The nature of the substance in yeast responsible for this reactivation effect is under investigation.

On the mode of action of chlorinating compounds P. K. STUMPF (by invitation) and D. E. GREEN *Depts. of Medicine and Biochemistry, College of Physicians and Surgeons, Columbia Univ., New York.* Chlorine and organic compounds containing active chlorine inactivate at very low concentrations a considerable number of enzymes e.g. triosephosphoric dehydrogenase, succinic oxidase and acetic oxidase. Other enzymes like catalase, transaminase and *d*-amino acid oxidase are not affected by these agents at the same concentration levels. In the case of the triosephosphoric dehydrogenase it can be shown that chlorine irreversibly oxidizes some sulfhydryl groups which are essential for the activity of the enzyme. In general those enzymes which are very sensitive to the action of chlorine are shown to depend for their activity upon the presence of sulfhydryl groups.

The oxidation of glucose by bacteria like *E. coli*, *Proteus vulgaris* and others is arrested completely in presence of low concentrations of chlorinating compounds. This effect is largely if not entirely due to the inhibition of the triosephosphoric dehydro-

¹ Stetten D. Jr. and Boxer G. E. *J. Biol. Chem.* 156: 271 (1944)

¹ Stumpf, P. K., and Green D. E., *J. Biol. Chem.* 153: 357 (1944)

genase. An exact parallelism has been found between the minimal concentrations of chlorinating compounds at which the oxidation of glucose is completely inhibited and the minimal concentrations at which bacterial growth is suppressed. The bacteriocidal action of chlorinating compounds can thus be accounted for quantitatively in terms of their irreversible inactivation of an enzyme which is an essential step in the metabolism of glucose. By contrast the viability of most bacterial spores does not depend upon the ability to oxidize glucose and consistent with this fact bacterial spores are found not to be killed by chlorine except at concentrations ten to twenty times greater than is necessary to kill bacterial cells—the permeability factor having been excluded.

Dietary requirements for fertility and lactation

XXXIII. Dried yeasts as sources of proteins and vitamin B complex for growth, reproduction and lactation. BARRETT SURF, *Dept. of Agricultural Chemistry, Univ. of Arkansas, Fayetteville.* *Brewers' Yeast (K)*¹. The brewers' yeast, fed at 30 to 40 per cent planes of intake, furnishing 11 to 18 per cent proteins, and which served as sources of the vitamin B complex, permitted growth in the first, second, third, and fourth generations at a rate equal to that obtained by feeding 15 per cent purified casein for a period of 4 months. Reproduction and lactation were excellent in the first, second, and third generations, the lactation efficiency being 85 to 95 per cent.

Cultured Yeasts. Growth in first and second generations on strains Kitchen Food, G, 90, 200, and 300, fed at 30 to 40 per cent planes of intake, furnishing 12 to 17 per cent proteins and vitamin B complex in the rations, was equal to that obtained on 15 per cent purified casein for a period of 4 months. Lactation efficiency varied with the strain of yeast, the Kitchen Food and strain G being the most efficient for rearing of young. The poorer results in lactation obtained with some of these cultured yeasts may be due to vitamin imbalances, since they are very abundant in thiamine and riboflavin, rather than to protein inadequacy.

Effect of experimental malaria on the electrophoretic pattern of the serum proteins of normal young men. HENRY LONGSTREET TAYLOR, GLENN FISCHER (by invitation), SAMUEL M. WELLS (by invitation) and ANCEL KEYS, *Univ. of Minnesota, Minneapolis.* Eleven normal young men were inoculated with the McCoy strain of tertian malaria. All subjects developed malaria which was terminated with quinine after the seventh or eighth paroxysm. The total number of degree hours of fever above 101°F, varied from 147 to 221 in the several individuals. Blood samples were drawn before inoculation and at the end of the last

paroxysm. The sera were dialyzed against veronal buffer (pH 8.6) and analyzed in the electrophoretic apparatus of Tiselius. Values for the separate components from both ascending and descending patterns were expressed as per cent of the total area. The mean total protein concentration of the sera, determined by micro-Kjeldahl, was 6.82 grams per 100 ml. before malaria and 6.76 after malaria. No qualitative difference in the electrophoretic pattern due to malaria appeared. The change in the various electrophoretic components, expressed as per cent of the corresponding values before malaria, was -12.9 for albumin, +23.2 for total globulin, +65 for the alpha one, +5.2 alpha two, +20.2 for beta globulin and +20.5 for gamma globulin. All changes except that of the alpha two globulin were statistically significant by the t test. A product moment correlation of 0.54 was obtained between the number of degree hours and the absolute increase in the alpha one component.

Crystalline aldolase and its identity with myogen A. JOHN FULLER TAYLOR, ARDA ALDEN GRIFFIN and GERTY T. CORI, *Depts. of Biological Chemistry and Pharmacology, Washington Univ. School of Medicine, St. Louis.* The enzyme aldolase has been obtained from rabbit muscle in several crystalline forms. 80 per cent of the enzyme in an aqueous extract is precipitated between 0.50 and 0.52 saturation by $(\text{NH}_4)_2\text{SO}_4$ at pH 7.5. The precipitate consists of fine needles which can be recrystallized from $(\text{NH}_4)_2\text{SO}_4$ at pH 7.5 as needles or, in some instances, as large well-formed six-sided plates. When the needles or plates are recrystallized from $(\text{NH}_4)_2\text{SO}_4$ at pH 5.8, hexagonal bipyramids are obtained which closely resemble myogen A, originally described by Baranowski.

When myogen A is prepared by a method which involves fractionation with $(\text{NH}_4)_2\text{SO}_4$ and with acetone, the bipyramids crystallized at pH 5.8 can also be converted to the needle form by crystallization at pH 7.5.

Irrespective of the method of preparation or of the crystal form, the protein has the same aldolase activity in a chemical or in an optical test. Assuming a molecular weight of 150,000, the turnover number corresponds to the splitting of 2300 moles of hexose diphosphate to triosephosphate per minute at 30° and pH 7.5. Aldolase crystallized from rat muscle by Warburg and Christian was reported to have about twice this activity. Under our conditions of testing, the crystalline rat aldolase prepared by us had the same turnover number as the rabbit muscle preparations.

Crystalline rabbit aldolase is electrophoretically homogeneous from pH 5.7 to 8.6. The isoelectric pH is 6.05. The mobility at pH 7.0 and 2° is 1.1×10^{-5} cm² sec⁻¹ volt⁻¹. Rat aldolase, also homogeneous, has a somewhat higher mobility and an isoelectric pH about 5.7.

¹ Strain K, Anheuser Busch, St. Louis, Mo.

Relation of fasting ketosis to the protein of the preceding diet HERBERT C TIDWELL (by invitation) and C R TREADWELL *Dept of Biochemistry, Southwestern Medical College, Dallas* The extra nitrogen excreted during a 2 day fast by rats previously on a 25 per cent protein diet (as compared with those on 5 per cent protein) was not eliminated by 3 days on a protein maintenance diet and 6 days of diuresis preceding the fast. A persistent excess of 8 mg of urinary nitrogen per square decimeter of body surface per day excreted during the fast by animals previously on the higher protein diet indicated this difference was not due to a lag in the nitrogen excretion.

A similar nitrogen value obtained by calculating the protein losses¹ in such animals during the fast appeared to confirm the conclusion that this nitrogen represented the catabolism of extra protein. However, the injection of a glucose supplement equivalent to the amount of antiketogenic material available from the excess protein catabolized after the higher protein diet failed to produce the antiketogenic effect that has been attributed to it. The greater fasting ketosis following a low protein intake appears to be related more to an increased utilization of carbohydrate in these animals than to the protein available for catabolism. This is evidenced by a more rapid disappearance of liver glycogen during the early fast and lower body stores than found in animals after higher protein diets with similar caloric intakes.

Distribution, retention, and excretion of radiophosphorus following thyroparathyroidectomy and the injection of parathyroid extract WILBUR R TWEEDY and (by invitation) MAX E CHILCOTE and MARY C PATRAS *Depts of Biological Chemistry and Physiology, Loyola Univ School of Medicine, Chicago* Other workers have observed a sharp decrease in the urinary excretion of P following thyroparathyroidectomy in dogs and parathyroidectomy in rats. In our experiments rats that were maintained on a diet of Purina chow were thyroparathyroidectomized and at various periods, ranging from 1 hour to 25 days after the operation, an experimental animal and its littermate control were injected intraperitoneally with 0.5 ml of a solution of Na_2HPO_4 representing 2 or 3 mg of P. After an interval of 18 hours the distribution, retention, and excretion of the labeled P were determined. A 50 to 75% reduction in the urinary excretion of radiophosphorus and a marked retention of radiophosphorus in the femurs, liver, and kidneys were observed 24 hours after thyroparathyroidectomy. During an 18 hour experimental period 1 week or more after

the operation, rats were found to excrete radiophosphorus in amounts approaching or exceeding the amounts excreted by their normal littermate controls.

Single doses of parathyroid extract (20 to 500 U S P units) injected subcutaneously into rats a few hours after thyroparathyroidectomy, and 1 hour before the administration of labeled P, greatly increased the urinary excretion of P³² to 10 units of parathyroid extract administered to rats 24 hours after they were thyroparathyroidectomized, and 20 minutes before the injection of labeled P, increased the urinary excretion of radiophosphorus 2-fold or more over the value found for their thyroparathyroidectomized controls.

Excretion of urinary corticoid hormones by man in health and disease ELEANOR H VERNING and J S L BROWNE (by invitation) *McGill Univ Clinic, Royal Victoria Hospital, Montreal, Canada* A highly sensitive bioassay method has been developed in our laboratory which permits the detection of corticoid activity in a 24 hour or 48 hour specimen of urine. This method is based upon the deposition of glycogen in the livers of glucose treated adrenalectomized mice and has been standardized against 17-hydroxy-11 dehydro corticosterone (Compound E), 1 glycogenic unit being equivalent to the activity of 1 microgram Compound E.

Using this method the excretion of corticoid hormones in normal men and women has been studied over periods of 15 to 30 days and the daily variations measured.

There is no cyclic variation in the excretion of these hormones and diet does not appear to have any influence on the output.

The excretion of corticoids has also been followed in various pathological conditions. In several cases of Addison's Disease the urinary corticoid activity was found to be either negative or at a very low level. This was also seen in cases of male and female panhypopituitarism. On the other hand 2 patients with Cushing's Syndrome excreted excessively high amounts of corticoids. There is an increased urinary excretion of these hormones following muscular exercise and damage such as surgical operation, infection or burns.

The administration of testosterone propionate tends to depress the excretion of these hormones. **Glutamic acid content of human blood serum** HEINRICH WAELSCH and BLANCHE A PRESCOTT (by invitation) *Dept of Biochemistry, New York State Psychiatric Inst and Hospital, New York* With a recently developed micro method (Federal Proceedings 1945) the conditions for the determination of free and bound glutamic acid in blood serum and plasma were studied. Glutamic acid and glutamine or pyrrolidon carboxylic acid

¹ MacKay, E M, Carne, H O, Wick, A N, and Vischer, F E *J Biol Chem* 141: 889 (1941)
² Addis, T, Poo, L J, and Lew, W *J Biol Chem* 115: 117 (1936)

may be separated by chromatographic analysis on aluminum oxide. By direct chromatographic adsorption of protein free serum filtrates the concentration of free glutamic acid was found to be in the range of 1 mg per 100 ml of serum. After hydrolysis of glutamine with 10 per cent trichloroacetic acid under conditions which liberate all of the amide nitrogen, only 10 to 20 per cent of the glutamic acid present in glutamine is determined. The conversion to glutamic acid of pyrrolidone carboxylic acid formed by the splitting of the amide necessitates an hydrolysis in 2N HCl at 90 to 95° for 1 to 2 hours. Under these conditions the protein free filtrate of blood serum of a limited number of normal individuals yielded values of 9 to 12 mg of glutamic acid per 100 ml of serum. The free glutamic acid comprises approximately 9 per cent of the values found after hydrolysis.

The concentrations of free and bound glutamic acid in protein free filtrates obtained by different methods were compared. Preliminary data on the changes of the glutamic acid concentration in serum after the administration of the amino acid are presented.

Studies on the metabolism of 2-acetylaminofluorene in rats. B. B. WESTFALL (by invitation) and H. P. MORRIS, *National Cancer Inst., Bethesda, Md.* Studies on the mechanism of carcinogenesis in rats following the ingestion of 2-acetylaminofluorene and related compounds have been carried out using a colorimetric method that detects minute quantities of the compound in protein-free solutions. The method depends on diazotization in strongly acid media and subsequent coupling under alkaline conditions with R-salt to give a red dye. This method has been applied to the determination of N-N-diacetyl-, N-acetyl-, and 2-aminofluorene after hydrolysis, and 2-nitrofluorene following reduction. It has been found that rats given the mono-acetyl compound orally in olive oil thrice weekly excreted in the urine 25-30% of the amount ingested during a 7-day interval. The compound appeared in a conjugated form 8-10 times more concentrated when calculated as the acetyl derivative than a saturated solution of the acetyl derivative in urine, indicating a change during metabolism that left the aminogroup still intact.

A study of urinary concentrations of the diazotizable urinary compound at various intervals following a single dose indicates a maximum absorption occurring 6-8 hours after ingestion. This excretion tapered off slowly thereafter and was practically completed in 72 hours. The diazotizable urinary material, after extraction with ether, was added to plasma. It could then be filtered through collodion membranes to at least 90 per cent. The ingested free-aminofluorene compound was found likewise to be excreted in a conjugated form in the urine.

Method for determining the affinity of avidin

for analogs of biotin. LEMUEL D. WRIGHT and HIRSH R. SKRAGS (introduced by L. Earle Arnow), *Sharp and Dohme, Inc., Glenolden, Pa.* Previous studies have demonstrated that large amounts of certain biotin analogs are capable of displacing biotin from the avidin-biotin combination. The present investigation has demonstrated that the relative affinity of avidin for biotin analogs possessing no microbiological activity *per se* may be determined readily. Such procedures involve the addition of avidin to tubes containing varying amounts of analog and an amount of biotin just sufficient to combine with the avidin employed. The uncombined biotin is measured microbologically with *Lactobacillus arabinosus* and is equivalent to the amount of analog taking part in the combination. The affinity of the compound under examination is expressed as the ratio of analog to biotin where one half of the biotin is combined with the avidin.

The affinity ratio for di-desethiobiotin is approximately 10. From a mixture of biotin methyl ester and the free acid the ester first combines with avidin. Several compounds possessing the urea ring but differing from biotin in other respects failed to combine with avidin. Thus while the cyclic urea ring is essential for a compound to combine with avidin the remaining structure of the molecule is a factor in modifying the affinity of avidin for such analogs.

2-Keto-D-gluconic acid in the polysaccharide of Irish moss. E. GORDON YOUNG and F. A. H. RICE (by invitation), *Dept. of Biochemistry, Dalhousie Univ., Halifax, Canada.* From the products of hydrolysis of a purified sample of carrageenin, the polysaccharide of Irish moss (*Chondrus crispus*), with oxalic acid under nitrogen, 2-keto-D-gluconic acid has been isolated as the di-isopropylidene derivative. The m.p. was 95° and $[\alpha]_D^{25} -48.8^\circ$. Micro-elementary analysis showed C, 52.99 and H, 6.81 per cent as against calculated values of 52.72 and 6.60 per cent. The anilide was prepared with m.p. 122° and $[\alpha]_D^{25} -28.9^\circ$. The physical constants of the methyl ester were m.p. 52° and $[\alpha]_D^{25} -43.9^\circ$. 2-Keto-D-gluconic acid was found to give the color reactions of fructose except the resorcinol test.

Further evidence for the presence of this compound was secured by exhaustive methylation of the polysaccharide, both before and after hydrolysis, in the isolation of the amide of the tetramethyl derivative. A crystalline product was obtained of the methylated polysaccharide showing the following characteristics, m.p. 130°-140° with decomposition, $[\alpha]_D^{18} +48.0^\circ$, OMe 15.2 per cent, ash 18.2 per cent.

By hydrolysis of carrageenin with hydrochloric acid in air some evidence was found for the formation of arabinose and arabinolactone as decomposition products of 2-keto-gluconic acid.

THE AMERICAN SOCIETY FOR PHARMACOLOGY AND
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THIRTY-SIXTH ANNUAL MEETING

Atlantic City, N J, March 11, 12, 13, 14, 15, 1946

(For possible corrections in any of the following abstracts see the next issue)

Central nervous system effects of anticholinergic agents BENEDICT E ABREU, ROBERT J TUFTS and MARJORIE E COUTOLENC *Division of Pharmacology and Experimental Therapeutics, Univ of California Medical School, San Francisco* The effects of three new spasmolytic agents, β diethylaminoethyl phenyl α thienylglycolate HCl, β -dimethylaminoethyl phenyl α thienylglycolate HCl and β piperidinoethyl α methyl p-venylacetate HCl have been compared with those produced by atropine sulfate, scopolamine HBr, pavatrine, trasentoin, amphetamine sulfate and sodium pentobarbital Unless otherwise specified, agents were administered intraperitoneally in 10 mg/kg doses, after the rat had been in the activity cage for at least one hour Changes in central nervous system activity were measured by a simple activity recorder in which all movements of the animal in a suspended cage were transmitted by tambour air recording to a kymograph

Uniform control effects produced by saline injections and manipulation were subtracted from those observed with various compounds For analysis of data, two arbitrary activity periods were selected These consisted of the first 55 minutes immediately following injection and return to the cage and the 27-minute interval following the first analysis period

Activity was measured during time of drug response and this was related to the total period of observation as a percentage of the whole Data for the two observation periods, shown consecutively, are as follows β diethylaminoethyl phenyl α -thienylglycolate HCl, +34, +19, β -dimethylaminoethyl phenyl α -thienylglycolate HCl, +28, +35, β piperidinoethyl α -methyl p-venylacetate HCl, -12, +13 atropine sulfate, +22, +41, scopolamine HBr, +54, +71, pavatrine, 0, -4, trasentoin, +1, +15, amphetamine sulfate (1 mg/kg), +37, +16, sodium pentobarbital (5 mg/kg), -19, +6 Preliminary studies, employing a more refined technique in which the amount of work performed by the animal is determined, indicate a similar trend with scopolamine HBr [Aided by a grant from Frederick Stearns & Company, Division of Sterling Drug Company, Detroit, Michigan]

Action of tetraethyl ammonium bromide on the mammalian neuromuscular system G H ACHESON and S A PEREIRA (by invitation) *Dept of Pharmacology, Harvard Medical School, Boston, Mass* The vasodepressor action of tetraethyl am-

monium has been shown to depend upon a blockage of vasoconstrictor nerve impulses at autonomic ganglia (Acherson and Moe, in press), by an action like that of curare at this site (Pereira and Acherson, this journal, 1946) Whether tetraethyl ammonium, like other quaternary ammonium compounds, has a true curariform action on frog muscle has been disputed Rothberger (Pflügers Arch 92 398, 1902) reported a decurarizing action in mammals

In cats under dial anesthesia, the responses of the calf muscles upon stimulation of the sciatic nerve, cut centrally, are relatively insensitive to tetraethyl ammonium Intraarterial doses of 10 mg may increase the twitch height as much as 20% Repeated 10 mg doses induce a gradual, long-lasting reduction of twitch height During tetanic stimulation doses of 1 mg or more cause a slight rise of tension followed by a fall, with slow recovery Fasciculation is produced only by 30 mg per kg or more injected intravenously The stimulating action of acetylcholine injected intraarterially is diminished and the blocking effect is increased by 10 mg doses

When the twitch height is reduced by curare ("Intocostin"), doses of 0.3 mg produce an increase in twitch height This effect is less striking than the decurarization by prostigmine and diminishes upon repetition

The influence of benzyl-imidazoline (priscol) on sympathomimetic vasoconstrictors and vasodilators RAYMOND P AHLQUIST and R A WOODBURY *Dept of Pharmacology, Univ of Georgia School of Medicine, Augusta* Benzyl-imidazoline (Priscol-Ciba) reverses epinephrine hypertensive phase to an hypotensive phase through an adrenolytic action (See Chess and Yonkman, These Abstracts, 4 114, 1945) The influence of Priscol on blood pressure and peripheral blood flow effects of other sympathomimetic drugs was studied in dogs Blood pressure was recorded by either a mercury manometer or a Hamilton manometer from the carotid or femoral artery Blood flow was measured in the femoral artery by means of a Rotometer The results before and after 10 mgm of Priscol are summarized below All doses are stated on a per kgm basis

Epinephrine, 5 gammas intravenous, marked pressor, 0.1 gamma intraarterial, marked constriction, after Priscol no pressor effect and sometimes a depressor phase, no effect or slight vasodilation in the leg

Ephedrine, 5 mgm intravenous, marked pressor; 0.1 mgm intra-arterial, slight constriction, after Priscol slight pressor effect and no effect on blood flow

2-methylamino heptane (EA-1, Billhuber), 5 mgm intravenous, marked pressor, 0.1 mgm intra-arterial, slight constriction, after Priscol very slight pressor and no effect on blood flow

1-(m-hydroxyphenyl) 2-methylaminoethanol (Neosynephrine-Stearns), 10 gammas intravenous, marked pressor, 0.1 gamma intra-arterial, vasoconstriction, after Priscol no effect on blood pressure or flow

Ethyl nor-suprarenin (Butanephrine-Winthrop), 0.3 mgm intravenous, marked depressor, sometimes with a pressor phase, 3 gammas intra-arterial, marked vasodilation, after Priscol only depressor and vasodilator effects without development of tachyphylaxis

1-(p-hydroxyphenyl) 2-isopropylaminoethanol (#277-Stearns), 0.1 mgm intravenous, depressor, 30 gammas intra-arterial, marked vasodilation, after Priscol depressor and vasodilator

From these results it is concluded that Priscol does not reverse sympathomimetic drugs but does inhibit the pressor and constrictor effects and has little action on the depressor and dilator effects [This study was partially supported by Ciba Pharmaceutical Co.]

The application of a graded type of response technique for the bio-assay of pituitary extract (posterior lobe) M. G. ALLMARK, W. M. BACHINSKI (by invitation) and C. A. MORRELL *Laby of Hygiene, Dept of National Health and Welfare, Ottawa, Canada*. A more efficient design for the bio-assay of pituitary extract (posterior lobe) is based on a graded response, using eight longitudinal strips of uterine muscle from one virgin guinea pig. Two dosage levels differing by a fixed percentage are used for both the standard and unknown preparations. Doses are added to the bath in a random order. The results have been calculated by a factorial analysis to obtain an estimate of the most probable potency of the unknown preparation and its standard error. The variations due to doses, muscle strips, group sensitivity and their interactions have been separated by the analysis of variance and their significance discussed.

Pharmacological properties of citrinin. ANTHONY M. AMBROSE and FLOYD DEEDS *Pharmacology Division, Bureau of Agricultural and Industrial Chemistry, U. S. Dept of Agriculture*. The preparation of pure citrinin and toxicity data for various laboratory animals by different routes of administration have been reported (Proc Soc Exptl Biol Med vol 59 Page 289, 1945). Certain data of pharmacological interest will be summarized here.

Citrinin administered intravenously to rabbits in

doses of 20 milligrams per kilogram of body weight produced marked miosis, dilatation of the ear veins, salivation and lacrimation which were not completely reversed by atropine. In the anesthetized dog (ether or barbitol) intravenous administration of citrinin produced an evanescent fall in blood pressure. Successive doses of citrinin revealed a rapidly developing tachyphylaxis. In the atropinized or vagotomized dogs the effect on blood pressure was reversed. The effect on respiration was inconstant. In some dogs there was evidence of slight respiratory stimulation of short duration while in others no effect was observed.

On the isolated frog or guinea pig heart small doses were without effect, while with large doses there was marked ventricular contraction. Subsequent doses of citrinin produced no effects.

On the isolated guinea pig lung citrinin invariably caused definite bronchial constriction which was relaxed by epinephrine. Repeated additions of citrinin to the perfusion fluid caused decreasing bronchoconstriction to a point where no further effect was demonstrable while the lung retained its response to histamine, acetylcholine or epinephrine.

On the isolated uterus tone was depressed, and on the isolated intestine tone was increased while in the intact animal (dog) both gastric motility and intestinal peristalsis were stimulated.

Intradermal injections of solutions of citrinin pH 7.2 in varying amounts showed no signs of local irritation or necrosis. On the conjunctiva of rabbits only a slight degree of conjunctivitis, of short duration was apparent.

No hemolytic or agglutinating effects were observed with citrinin in concentrations up to 20 mgm per cent.

Pharmacologic properties of p-carbamido-phenylarsenous oxide.¹ HAMILTON H. ANDERSON, VICTOR P. BOND and BENEDICT E. ABREU *Division of Pharmacology and Experimental Therapeutics, Univ of California Medical School, San Francisco*. p-Carbamidophenylarsenous oxide,² the trivalent analog of carbarsone (p-carbamidophenyl arsonic acid) has been shown to have greater activity *in vitro* and *in vivo* against *E. histolytica* than the pentavalent compound (Anderson, H. H. and Hansen, E. L., in press). For this reason studies of the toxicity, distribution and other pharmacologic properties of the arsonic oxide were undertaken.

On intragastric administration of 2% suspensions in 10% acacia in water to rats, the LD₅₀ was 510 ± 40 mg/kg. Gastric irritation and hemorrhage fol-

¹ The work described in this paper was done under contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of California.

² Supplied by the Lilly Research Laboratories, Indianapolis, Indiana.

lowed administration of lethal amounts, but were less marked when equal parts of propylene glycol and water were used as solvent. A short term toxicity test (described by Carl C. Smith) was made using $\frac{1}{10}$, $\frac{1}{5}$ and $\frac{1}{2}$ of the LD_{50} dose, daily for 11 times. Rats did not lose weight and exhibited no signs of toxicity nor damage to the gastro enteric tract. Studies of excretion revealed that appreciable amounts of arsenic were present 9 days after the last intragastric dose. Studies of distribution in rats, rabbits and monkeys indicated that tissues containing the largest amounts of arsenic were, in descending order, liver, kidneys, lungs, spleen, large bowel, stomach and blood, as well as bile, feces and urine. The micro method of Cassil and Wichman (*J. Offic. Agric. Chem.* 22: 436, 1939) was used after subjecting samples to wet acid digestion. The arsine oxide contained 32.0% arsenic.²

Rabbits died after 20 to 40 mg./kg. had been given intravenously, although oral doses of 75 mg./kg. were tolerated. Daily oral doses of 2.2 and 5.3 mg./kg. in enteric tablets given for 34 days did not alter weight, hepatic nor renal functions. After 22 days one animal given 13.3 mg./kg. daily died. Congestion of the liver, kidneys and lungs was observed.

Monkeys tolerated daily oral doses of 11, 17 and 27 mg./kg. in enteric tablets given for 45 days without impairment of hepatic or renal function nor weight loss. Natural infections of *E. histolytica* were cleared for 6 months.

In man daily doses of 30 and 60 mg., in enteric tablets, were tolerated for 10 days without evidence of dysfunction.

p-Carbamidophenylarsenous oxide deserves further study as an amebicide.

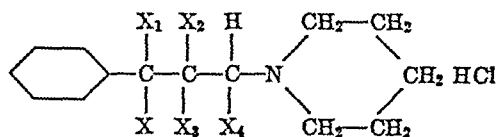
The action of fumariaceous alkaloids. ROBERT C. ANDERSON (by invitation) and K. K. CHEN, *Lilly Research Lab., Indianapolis*. Manske, in an exhaustive investigation of Fumariaceous plants, isolated numerous alkaloids and elucidated their structures (*Canad. J. Res.* 7: 258, 1932; *J. Am. Chem. Soc.* 67: 95, 1945). Through his courtesy, 15 alkaloids were made available to us for a pharmacologic study. Their names and LD_{50} 's in mice by intravenous injection are as follows:

	mg. per kg.
Protopine HCl	35.9 ± 1.90
Adlumidine	37.2 ± 0.77
Isocorydine HCl	49.5 ± 0.90
Capnoidine	29.1 ± 2.80
Capaurine	55.8 ± 7.40
Capaundine	62.4 ± 5.36
Corydaline	135.5 ± 12.80
Ophiocarpine	138.7 ± 4.10
Ochotensine	10.6 ± 0.54
Chelidomine	34.6 ± 2.44
dl-Canadine	76.8 ± 3.69
l-Isocorypalmine	132.6 ± 5.00
d-Tetrahydro-palmatine HCl	126.0 ± 4.96
dl-Tetrahydro-palmatine HCl	121.6 ± 6.65
l-Tetrahydro-palmatine HCl	110.9 ± 7.53

Capnoidine and l-isocorypalmine produced catalepsy in young monkeys as measured by the hanging response described by Richter and Patterson (*J. Pharmacol. & Exper. Therap.* 43: 677, 1931), while other alkaloids in the same animals did not cause this effect. All the compounds stimulated the isolated guinea pig's or rabbit's uterus. Capsurine, capauridine, isocorydine, ochotensine, and capnoidine inhibited the isolated rabbit's intestines. Protopine, corydaline, and l-isocorypalmine produced stimulation of intestines in weak concentrations but inhibition in strong ones; the remaining alkaloids were all stimulating. Fall of blood pressure was observed in etherized cats following intravenous injection of each alkaloid. The 3 optical isomers of tetrahydro-palmatine were found to differ only slightly from one another in their pharmacologic effects.

The antispasmodic activity of substituted phenyl propyl piperidines. T. J. BECKER, ESTELLE ANANENKO (by invitation), GWENDOLYN GLENWOOD (by invitation) and L. C. MILLER, *Research Lab., Winthrop Chemical Co., Inc., Rensselaer, N. Y.* A series of substituted phenyl propyl piperidines have been compared *in vitro* for their ability to reduce spasms elicited in smooth muscle by barium chloride, acetylcholine and histamine. This series is of interest since none of the compounds are esters, all of them being either amines or amine alcohols. Spasms were induced by barium chloride and acetylcholine in strips of rabbits' ileum and by histamine in guinea pigs' ileum. The acute intravenous LD_{50} of each compound has been determined in mice.

The basic structure of the twenty compounds tested is:



X = H, C_6H_5 , or C_6H_{11}

X = H or OH

X₂ = H, CH_3 , or CH_2CH_3

X₃ and X₄ = H or CH_3

A previously unpublished method of evaluating the data of the antispasmodic tests afforded a quantitative comparison with atropine and papaverine for the neurotropic and musculotropic effects, respectively. Thus the activity of the compound where X, X₁, X₂, and X₄ equal H and X₃ equals CH_3 was found to be 120 per cent of that of papaverine and 0.66 per cent that of atropine. When X was substituted by C_6H_5 , the activity was found to be 180 per cent that of papaverine and 0.66 per cent that of atropine. Further, if X was now substituted by C_6H_{11} , the musculotropic activity increased still

more, being 910 per cent that of papaverine, however, a loss in the neutropic activity was suffered, the cyclohexyl compound having only 0.32 per cent of the activity of atropine. The effect of further substitutions on the basic structure will be discussed.

The pharmacology of a new series of choline salts. **FREDERICK K. BELL** (by invitation), and **C. JELLETT CARR**, *Dept. of Pharmacology, School of Medicine, University of Md.* The nitrate ester of choline perchlorate was prepared during an investigation of choline compounds in a plant extract. The paucity of information on the inorganic esters of this important base and the stability of the perchlorate salts of choline prompted an investigation of these compounds. The perchlorate salts occur as white crystalline substances having sharp melting points. They are non-hygroscopic and are easily purified by recrystallization from hot water or alcohol. Pharmacologically these salts are qualitatively similar to choline and acetylcholine. Acetylcholine perchlorate is equally as potent as a depressor as acetylcholine chloride and is more stable in solution or as the dry crystalline form. The nitrate ester of choline perchlorate is approximately one-half as potent as acetylcholine. This compound is not affected by choline esterase. In varied experiments on smooth muscle of the rat, on the eye of the rabbit and on the blood pressure of the dog these salts compare favorably with the chlorides or bromides of choline and acetylcholine and in addition are more stable. It is suggested that because of their physical stability these salts may find applications in therapeutics.

In vitro development of *P. falciparum* gametocytes. **ROBERT W. BERLINER** (introduced by James A. Shannon), *Research Service, Third Medical Division, Goldwater Memorial Hospital, and the Dept. of Medicine, New York Univ. College of Medicine, New York*. (Read by title.) Incidental to the development of a technique for the *in vitro* examination of antimalarials using *Plasmodium falciparum* it was observed that under certain conditions as much as 90% of the total parasite population may develop into gametocytes. The factors concerned with the development of sexual from asexual parasites have not yet been fully elucidated. It is clear, however, that the duration of the blood-induced infection in the parasite donor is not important. Several physical and chemical factors influence the number of gametocytes that may develop. Gametocyte production, for instance, is greater in cultures maintained at 37°C than at 39.5°C and greater in the plasma of certain individuals than in that of others.

Since the original parasites in the cultures are only young ring forms, it is clear that the gametocytes are derived from the asexual cycle, any ring form having this potentiality for differentiation.

This differentiation takes place at an early stage, since immature sexual forms are sometimes distinguishable at 24 hours. At 48 hours morphological differentiation is distinct. Although the trophozoites do not survive beyond a single 48 hour cycle, the maturation of the gametocytes continues for seven to ten days, at which time the gametocytes have developed to a stage indistinguishable from that normally seen in the peripheral blood of patients with falciparum malaria. This development time corresponds closely to the interval between the appearance of trophozoites and gametocytes in clinical malaria due to this strain of *P. falciparum* (Casta). [*Based upon work done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and New York Univ.*]

The *in vitro* assay of suppressive antimalarial activity. *P. falciparum*. **ROBERT W. BERLINER** (introduced by James A. Shannon), *Research Service, Third Medical Division, Goldwater Memorial Hospital, and the Dept. of Medicine, New York Univ. College of Medicine, New York*. (Read by title.) A method for assaying activity *in vitro* should be useful as an adjunct in the study of the mode of action of antimalarial drugs. By this means the effectiveness of a drug may be evaluated without interference from products of its metabolism which themselves may possess antimalarial activity. The latter products may be studied separately with amounts much smaller than those required for *in vivo* testing.

For this purpose, parasites have been grown by a modification of the method of Bass and Johns. Plasma enriched with glucose is placed in small, flat-bottomed test tubes. The bottom of the tube is covered with a thin layer of red cells parasitized with *P. falciparum*. The drug to be tested is added in varying concentrations to the plasma. Several tubes without drug are included as controls in each experiment. The tubes are placed in a water bath at 39.5 degrees C in an atmosphere of 5% CO₂, 95% air. Specimens for examination are withdrawn at 24 and 48 hours. Differential enumeration of the parasites from control tubes shows growth and maturation of the parasites, with segmentation in a considerable proportion. Reinvasion of red cells and multiplication of the parasites have not been observed.

Many drugs known to have antimalarial activity, when added to this preparation, produce inhibition of the normal maturation of the parasites. The smallest detectable inhibition generally occurs at a plasma drug concentration of the same order as that known to be effective *in vivo* in patients infected with the same strain of parasites. [*Based upon work done under a contract recommended by the Committee on Medical Research, between the*

Office of Scientific Research and Development and New York Univ]

Concentration technique for detection of trophozoites of human malaria ROBERT W BERLINER (introduced by James A Shannon), FREDERICK S BIGELOW, (by invitation), and THOMAS J KENNEDY, JR *Research Service, Third Medical Division, Goldwater Memorial Hospital, and the Dept of Medicine, New York Univ College of Medicine, New York.* (Read by title) A method for the concentration of malaria parasites utilizing 30% albumin solutions has recently been described by Ferrebee. This method has been modified to permit the detection of *P. vivax* at a density below 100 parasites per cubic centimeter of blood. This is in contrast with the usual thick smear technique for which approximately 10,000 parasites per cubic centimeter are required. The method depends on changes in the density of the red blood cell produced by the parasite. Consequently, it is of no value in the concentration of *P. malariae*, nor, under ordinary circumstances, of *P. falciparum*. However, preliminary studies indicate that the parasites in blood infected with *P. falciparum*, when incubated 24 hours in vitro, can be concentrated to an extent approaching that attainable with *P. vivax*.

The subinoculation of 200 ml of blood to uninfected individuals has been used by Fairley for the detection of parasites at submicroscopic densities, to distinguish prophylactic from suppressive action. The concentration technique, studied as a substitute for subinoculation under similar conditions, has been found satisfactory for this purpose. By the application of either the concentration method or the subinoculation technique parasites can be found 8½ days after heavy inoculation with sporozoites in untreated individuals and in patients receiving full therapeutic doses of quinine or the highly effective SN 7618, 7-chloro-4-(4-diethylamino-1-methyl butylamino)quinoline. The concentration method has obvious advantages over the subinoculation technique [Based upon work done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and New York Univ]

Pamaquin 1 Curative antimalarial activity in vivax malaria ROBERT W BERLINER (by invitation), JOHN V TAGGART (by invitation), CHARLES G ZUBROD, (by invitation), WILLIAM J WELCH, (by invitation), DAVID P EARLE, JR (by invitation) and JAMES A SHANNON *Research Service, Third Medical Division, Goldwater Memorial Hospital, and the Dept of Medicine, New York Univ College of Medicine, New York.* (Read by title) The experiments of James, recently confirmed by Watson et al., indicate that pamaquin has prophylactic activity against infection with *P. vivax*. Work by Sinton, Dixon and others indicates that pamaquin also has some curative action on this

type of malaria. The value of pamaquin for either use as a routine measure is limited by high toxicity. However, as a lead for the synthesis of new compounds possessing similar activities a reexamination of pamaquin seemed indicated. Studies of the toxicity of pamaquin, its suppressive activity in vivax and falciparum infections, and its curative activity in vivax malaria have been performed.

The curative activity of pamaquin has been studied using a strain of *P. vivax* (Chesson) originating in the Southwest Pacific. Treatment with quinine of primary attacks due to this strain is following by relapse within three months in more than 80% of cases. Nine patients who received daily doses of 90 mg of pamaquin and 2 grams of quinine simultaneously for 14 days have had no relapses in the nine months following their primary attacks. Relapses have occurred in patients receiving 90 mg of pamaquin daily followed by quinine and in patients receiving daily doses of 30 mg of pamaquin and 2 grams of quinine simultaneously. The latter groups are too small for comparison of their relapse rates with that of the controls. [Based upon work done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and New York Univ]

Cinchona alkaloids 1 Appraisal of suppressive antimalarial activity ROBERT W BERLINER (by invitation), JOHN V TAGGART (by invitation), CHARLES G ZUBROD (by invitation), WILLIAM J WELCH (by invitation), DAVID P EARLE, JR (by invitation) and JAMES A SHANNON *Research Service, Third Medical Division, Goldwater Memorial Hospital, and the Dept of Medicine, New York Univ College of Medicine, New York.* The suppressive antimalarial activity of a drug is that which is exerted against the erythrocytic forms of the parasite. This activity is amenable to quantitative appraisal using standardized blood-induced infections.

Blood-induced vivax (McCoy strain) malaria is established in wholly susceptible patients and after 4 days of fever, the agent under study is administered so as to approximate constant plasma drug levels for 4 days. The effect is then measured by analysis of the subsequent course of temperature and parasitemia. Three classes of effect are possible. Class I—no effect, Class II—partial or complete temporary disappearance of fever and/or parasitemia, Class III—"cure," i.e., complete disappearance of fever and parasites for 14 days, followed by recurrence of clinical malaria after reinoculation with same strain of malaria.

The antimalarial effect of various plasma quinine levels was studied in 30 patients. Plasma quinine 4 mg per liter or higher = 11 Class II effects and 1 Class I effect, 2-4 mg per liter = 13 Class II effects and 1 Class I effect, below 2 mg per liter = 4 Class I effects. The critical plasma quinine level

dividing Class II and Class III effects is, therefore, between 4 and 5 mg per liter. These results constitute a reference standard for measurement of relative suppressive antimalarial activity. The test object is highly stable [Based upon work done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and New York Univ.]

The effect of methyl xanthines on urea excretion in rabbits. FREDERICK BERNHEIM (with the technical assistance of Helen R. Field) 2 kg rabbits were kept in nitrogen equilibrium by feeding 500 grams of carrots and a cabbage leaf a day. They excreted 0.9-1.0 grams of nitrogen and 0.7-0.8 grams of urea nitrogen daily. When 100 mg of caffeine citrate were injected subcutaneously twice a day for two days, the total and urea nitrogen rose slightly after the first day, then dropped to 0.5 and 0.4 gram respectively, and then gradually returned to normal over a three day period. When 100 mg of theobromine or theophylline were injected, no rise occurred after the first day and a drop to 0.3 and 0.25 gram occurred after the second, followed by recovery. Food consumption and urine volume remained constant. Allantoin, ammonia, and creatinine excretion were essentially unchanged. 250 mg of pentnucleotide gave similar but not as marked results. These experiments differ from those previously reported in that the food intake was kept constant and the diet produced an alkaline urine.

Induction in mice of increased resistance to a lethal toxin of hemolytic streptococcus. ALAN W. BERNHEIMER (by invitation) and G. L. CANTONI. Dept of Bacteriology, New York Univ. College of Medicine, New York, N. Y. and the Dept of Pharmacology, Long Island College of Medicine, New York, N. Y. It has been shown previously that application to the isolated frog's heart of partially purified culture supernates containing the oxygen-labile hemolysin of hemolytic streptococcus causes the heart to release a substance which inhibits the cardiotoxic and lethal effects of the preparation employed (J. Exp. Med. 81: 307, 1945). In continuation of this work we have looked for a parallel effect in mice. If mice respond in a manner analogous to that of the frog's heart, it seemed possible that the injection of a sublethal dose of toxin would confer protection against a lethal dose injected at a later time.

Extensive experiments have shown that the injection of a sublethal dose of toxin induces a slight but significant degree of protection. The protective response does not come on immediately but can be demonstrated within 6 hours after injection of the toxin. It persists for 28 to 40 hours after which time the mice are again fully sensitive to the toxin. The nature and specificity of the protective effect are being investigated [Aided in part by a grant from the Dazian Foundation for Medical Research].

Mechanism of action of calcium on the nervous system. T. C. BARNES and R. BEUTNER. Depts of Pharmacology and Physiology, Hahnemann Medical College and Hospital of Philadelphia. (Read by title.) Four cubic centimeters of 5% cholesterol in guaiacol was placed in the cup of the oil cell immersed in 200 c.c. of 0.9% NaCl (Biodynamica 4: 47, 1942; J. Exp. Med. Surg. 3: 325, 1945; Fed. Proceed. 1946). 0.05% acetylcholine produced a phase boundary potential of 35 mv. negative (model of action current in nerve). 1 gram of CaCl_2 was ground in a mortar with 100 c.c. of the 5% cholesterol in guaiacol and the mixture placed in an oil cup. The outer saline contained 0.03% CaCl_2 in 0.9% NaCl. 0.05% acetylcholine produced 20 mv. negative (compared with 35 mv. in absence of calcium).

The experiments suggest that the action current in nerve is a phase-boundary potential produced by acetylcholine. The blood calcium level determines the ability of acetylcholine to dissolve in the nerve lipid and produce action currents. According to Feldberg (Physiol. Rev. 25: 596, 1945) acetylcholine acts on nervous tissue by its electrical potential (previously demonstrated in the oil cell). The experiments above explain the empirical observation of Bronk (J. Neurophysiol., 2: 380, 1939) that calcium can block synaptic transmission.

The occurrence of considerable acetylcholine potential in high calcium explains the persistence of the spike potential under similar conditions. Traces of inorganic ions do not have electrical effects in high concentration of NaCl of blood. Calcium can decrease solvent properties of lipid [Aided by grant from American Philosophical Society].

The cardiac toxicity of injectable local anesthetics. R. BEUTNER, Dept of Pharmacology, Hahnemann Medical College. (Read by title.) Schamp, Schamp and Tainter maintained that monacaine is four times more toxic than procaine for the cardiovascular system, although both drugs are equally toxic to the respiration. This assertion was reached by comparing the mean fatal doses of these two drugs in various animals respiring normally with the fatal doses in cats after artificial respiration. In naturally respiring animals death is due to respiratory failure, under artificial respiration cardiac failure is assumed to be the cause but this is a doubtful assumption. Experiments have, therefore, been performed on the isolated heart of rabbits using a new improved technique by which the isolated heart was kept beating for 10 hours. Details of this method will be described later by its originator.

Addition of procaine HCl 1:100,000 had no effect on the amplitude of heart beat, monacaine HCl 1:50,000 diminished the amplitude to one-half. Monacaine had a slightly more damaging effect in that 1:100,000 diminished the amplitude to somewhat less than one-half. As judged by the relation

of diminution of cardiac amplitude by either drug, monacaine is not quite twice as cardiotoxic as procaine. However, on the average, monacaine is 1 2 to 1 5 times more potent an anesthetic than procaine (Tainter). Therefore, the somewhat greater cardiotoxicity of monacaine is nearly parallel to its greater anesthetic potency.

The blood pressure lowering effect of local anesthetics used for injection R. BEUTNER and W. C. DIETRICH (by invitation), *Dept. of Pharmacology, Hahnemann Medical College of Phila.* (Read by title). The fall of arterial blood pressure after spinal anesthesia with procaine is largely the result of peripheral vasodilation although other factors play a secondary role (B. Kisch, 1943). Accordingly it was found that procaine injected intravenously in dogs which had been anesthetized with morphine and chlorotone and atropinized (1 mg./kg.), lowers the blood pressure 14 to 32 mm., this was observed in 5 dogs. This drop lasted only for 2 to 3 minutes and returned to normal thereafter. In contrast, monacaine, a recently introduced isomer of procaine, in doses of 10 mg./kg. injected intravenously in the same dogs, either was found to leave the blood pressure unchanged (as observed in 3 dogs), or it caused a temporary rise (as observed in one dog 31 mm. after 10 mg./kg. lasting 2 minutes, subsequently after 2 mg./kg. of monacaine a rise of 8 mm. lasting 1 minute, in another dog the blood pressure fell after monacaine, but this was not reversible and must be considered as central depressant effect—the dog died shortly afterwards).

Most of the stronger local anesthetics also lower the blood pressure (to be described in detail later), excepting cocaine which however is unsuitable for injection due to its toxicity and narrow margin between toxic and anesthetic dose. According to our observations made so far monacaine seems to be the only local anesthetic which does not lower the blood pressure by peripheral vasodilation, and is also suitable for injection.

The least irritant of the commonly used topical anesthetics R. BEUTNER and W. C. DIETRICH (by invitation), *Dept. of Pharmacology, The Hahnemann Medical College and Hospital of Philadelphia*. Solutions of well known local anesthetics in various concentrations were instilled in the left eyes of rabbits every 15 minutes for eight hours continuously, or less if severe irritation was noted before eight hours had elapsed. For control, distilled water was instilled in the eyes of 3 rabbits, a slight irritation was noted. Only irritation greater than that of water was considered. Furthermore in order to check the sensitivity of the rabbits' eyes the right eye of the test rabbit was always treated with metycaine 5 or 10%. This local anesthetic was selected as standard because it proved to be the least irritant one of all local anesthetics active on topical application to the eye. The ratio of the high-

est non-irritant concentration to the minimal anesthetic concentration was determined as follows: metycaine 44, diothane 24 (approximately), cocaine 22, butyn 6 5, tetracaine (pontocaine) 5, intracaine 4, nupercaine 5 to 50. The higher this ratio, the more desirable is the local anesthetic for topical application. (The "minimal" anesthetic concentration is the one producing an anesthesia lasting only 10 minutes, (Beutner and Calesnick). The above given ratio is hard to define for nupercaine since its minimal anesthetic concentration is subject to subtle influences, the slightest change in pH in either direction causes nupercaine to become very much less effective, hence raises the minimal anesthetic concentration (Beutner and Bradlow, *Federation Proceedings*, March, 1943).

Methemalbuminemia during combined therapy with pamaquine and quinine WILLIAM D. BLAKE (by invitation), CHARLES G. ZUBROD (by invitation), and MORRIS ROSENFELD *Research Service, Third Medical Division, Goldwater Memorial Hospital and the Dept. of Medicine, New York Univ. College of Medicine, New York*. A brown pigment, identified as methemalbumin, has appeared consistently in the serum of patients receiving pamaquine and quinine in combination for the treatment of malaria. It is noteworthy that this disturbance in metabolism of the blood pigments did not arise in patients receiving either of the two drugs alone in the same dosage.

The pigment has heretofore been only roughly estimated on the basis of its absorption at 623 mμ. A far more intense absorption band at 405 mμ noted in the present study proved to be more suitable for quantitative measurement. Hematin added to serum in vitro yields the hematin albumin complex for which a tentative value of the molar extinction coefficient may be given as $\sum_{405m\mu}^{mol} = 7.5 \times 10^4$ calculated per mol of hematin iron.

Methemalbuminemia progressively increased during 14 days of combined therapy with pamaquine, 90 mg./day, and quinine, 2 grams/day. At the close of therapy serum levels in six patients ranged from 6 to 45 mg. of hematin per liter with an average of 30 mg. per liter.

Concurrent disturbances in pigment metabolism consisted in methemoglobin production in the red cells, increased fecal excretion of urobilinogen, and increased fecal and urinary coproporphyrin. Measurements on methemalbumin time curves in serum following intravenous injection of hematin and hemoglobin are in progress. [Based upon work done under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and New York Univ.] 13-2-4-46—FP 5541 p. 748 Take 2-8-5d Gal. 6.

The determination of the most efficient response for measuring drug potency C. I. BLISS and B. L. BARTELS (by invitation) *Yale Univ. and Connecti-*

cut Agricultural Experiment Station, New Haven, Conn. In many experiments several responses are available for measuring drug potency. The most efficient is that for which the dosage response curve has the steepest slope (b) relative to the standard deviation (s) about the curve. Instead of choosing a single response with a minimal ratio s/b from several possibilities, it is sometimes more efficient to use a weighted average of two or more measurements of the same basic reaction. The most efficient combination can be determined by the statistical device known as the discriminant function.

The technique is illustrated with the data from experiments on several drugs. A re-examination of data on the rabbit assay of insulin from hourly readings of the blood sugar shows that the different intervals are markedly unequal in the information they provide on the potency of insulin. The application of this method to more extensive data should provide a revised bleeding schedule which would be both simpler and more efficient. Data on the assay of ergometrine and of androsterone yield similar results.

Liver injury and its influence upon the acetylcholine splitting activity of rat and dog. R. W. BRAUER and M. A. ROOT (introduced by O. Kraye), *Dept. of Pharmacology, Harvard Medical School, Boston, Mass.* The acetylcholine splitting activity of rat and dog plasma was followed after carbon tetrachloride administration (0.5-0.85 cc per kg intraperitoneally in rats, orally, in 1 volume of vegetable oil in dogs, administered every other day).

In growing rats during the period of most rapid growth (and for a week thereafter), plasma esterase levels and erythrocyte counts increase steadily, cholinesterase activity per red cell remains unchanged.

Carbon tetrachloride arrests growth, or, in older animals, causes weight loss. After a latent period of three days plasma esterase activity decreases and is greatly depressed on the seventh day in comparison with control animals of the same age or the same weight. Erythrocyte counts or cholinesterase activity per cell do not change as a result of carbon tetrachloride administration.

In dogs, carbon tetrachloride produces an initial rise of plasma esterase, followed by a slow, irregular fall.

Portal obstruction produces a gradual decline of esterase to a lower level.

Liver function tests indicate severe liver damage from the carbon tetrachloride, but not from portal obstruction.

These results suggest a relation between the production of the acetylcholine splitting enzyme of mammalian plasma, and liver function.

Cinchona alkaloids. 4 Metabolic products in human urine. BERNARD B. BRODIE, JOHN E. BAER

(by invitation), and LYMAN C. CRAIG, *Research Service, Third Medical Division, Goldwater Memorial Hospital, and the Dept. of Medicine, New York University College of Medicine, New York*, *Rockefeller Inst. for Medical Research*. Metabolic products of each of the principal cinchona alkaloids have been isolated from human urine. The separation of the products from each other and from the parent drug was based on differences in their partition coefficients in different systems. The metabolic products studied to date are increasingly more water soluble with progressive metabolism. This has permitted preliminary separations by successive extraction of alkalinized urine with solvents of progressively higher polarity, viz., heptane, ether and isomyl alcohol. Separation of products in each of these fractions may then be made by an 8 plate counter-current distribution procedure (Craig). Completeness of separation may be rechecked by a multiple plate counter-current distribution procedure (Craig). Final purification and isolation may be achieved by recrystallization from appropriate solvents. The following products have thus far been isolated and partially characterized.

From Cinchonine,

$C_{19}H_{21}O_2N_2$ —MP 268-270. Characterized as 2 hydroxy cinchonine (J. B. Koepfli).

$C_{19}H_{21}O_3N_2$ —MP 278-79. Ultraviolet absorption suggests this compound is a derivative of 2 hydroxy cinchonine with the additional oxygen in the quinuchidine portion of the molecule.

From Quinidine,

$C_{20}H_{24}O_2N_2$ —MP 235-60 not sharp. Solubility characteristics and ultraviolet absorption suggests it is 2 hydroxy quinidine.

$C_{20}H_{24}O_3N_2$ —MP 209-11. Solubility characteristics and ultraviolet absorption suggest it differs from quinidine because of an oxygen in the quinuchidine portion of the molecule.

Several other products have been isolated in the case of quinine, quinidine and cinchonidine. Ultraviolet absorption indicates that both quinine and cinchonidine form 2 hydroxy derivatives but there are, as yet, insufficient data to characterize these products. [Based upon work done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and New York Univ.]

Chemotherapy of tuberculosis. I. Thymol in experimental tuberculosis in the guinea pig. CLYDE BROOKS, *Dept. of Pharmacology, Essex College of Medicine and Surgery, Newark 4, N. J.* Guinea pigs were inoculated with adequate doses of a virulent strain of human tubercle bacilli. Then they were divided into three groups. I, was untreated, II, was treated with thymol from the time

of inoculation, III, was treated with thymol beginning three weeks after inoculation

All three groups were studied until results could be determined

It was found that the thymol had no obvious injurious effects on the animals

The treated animals lived longer and maintained their weight better than the untreated controls. Animals which were treated early (group II) lived longer, and maintained weight better than animals treated late (group III)

Pathological observations on the bodies of the animals showed that the animals treated with thymol had less extensive tuberculosis than the controls, and also that those treated early had less extensive tuberculosis than those treated late

The results indicate that thymol has a restrictive effect on experimental tuberculosis in the guinea pig

In general, these results are in accord with those published by my former colleagues at the Univ of Alabama. Ralph McBurney, Harvey Searcy, and Louise Cason (*Jour of Laby and Clin Med* 30 32, 1945)

Use of the latent period in studies on the agent of chicken tumor I W RAY BRIAN (by invitation) *National Cancer Inst, National Inst of Health, United States Public Health Service*. The time elapsing between inoculation of chicken tumor I (Rous) agent and the appearance of a tumor at the site of inoculation, i.e., the latent period, is a function of the concentration of agent. When the latent period is transformed to its reciprocal and the dosage of agent to its logarithm, a straight line relationship is obtained between these two functions, also, the variance of the transformed responses is essentially the same at all dosage levels. These transformations of the data, therefore, permit the analysis of results obtained with the agent of chicken tumor I by simplified statistical procedures

Since multiple inoculations of agent can be made on each experimental chicken, the precision of bioassays can be increased by use of a balanced experimental design and the segregation of variations arising from different sources

On the specificity of histamine and on the role of potassium in a loss of contractility of the intestinal smooth muscle of the guinea pig G L CANTONI and G EASTMAN (by invitation) *Depts of Pharmacology, Long Island College of Medicine and New York Univ College of Medicine*. The isolated ileum of the guinea pig suspended in Tyrode's solution loses its capacity to contract in response to administration of histamine following administration of this drug in large doses (Barsoum, G S and Gaddum, J H, *J Physiol* 85 1, 1935). This effect has been considered specific for histamine, is used in fact to identify it pharma-

cologically, and is attributed to blocking of special receptors on the effector cell

The investigations here reported, however, reveal that this effect is not specific for histamine but exhibited also by a number of other unrelated agents capable of stimulating intestinal smooth muscle. The response of the intestinal strip to a previously effective dose of acetylcholine, pilocarpine, and barium chloride is considerably diminished following a maximal contraction produced by any of these drugs. This condition of decreased contractility lasts about 30 minutes and is completely reversible

The intestinal strip reacts quite differently to a maximal contraction produced by potassium chloride. This contraction is not followed by a period of decreased response to a previously effective dose of histamine or acetylcholine but rather by a period of increased response to these and other agents. A smaller increase in the concentration of potassium of the perfusion fluid, which does not by itself initiate a contraction of the intestinal strip, is capable of abolishing the state of temporary refractoriness which, as indicated above, follows a large contraction produced by histamine, acetylcholine, etc. The investigation is being extended to study with iodoacetate and other enzyme poisons, the possible explanation of the nature and site of this action of potassium. [Aided by a grant from the Committee on Therapeutic Research, Council on Pharmacy and Chemistry, A M A]

The effect of thiamine-deficiency, quinidine, hyperthyroidism and hypothyroidism on the adenosinetriphosphate content and the adenosinetriphosphatase activity of the heart muscle of rats GRAHAM CHEN and E M K GELLING *Dept of Pharmacology, The Univ of Chicago*. On a thiamine free diet rats which had developed severe deficiency symptoms and pathology of the myocardium, showed a considerable decrease both in the A T P content and in the phosphatase activity of the heart muscle

In the heart muscle of rats, receiving quinidine orally (100 mg/kg twice daily) more than a week, a slightly higher content of A T P was obtained. There was no change in the adenosine triphosphatase activity of such a heart muscle. The increase of the amount of A T P in the myocardium appears to have occurred sometime after the electrocardiographic modifications, (prolongation of Q T interval and bradycardia) were produced by quinidine

There was no significant difference in A T P concentration and in the phosphatase activity of the myocardium of rats 30 to 70 days after thyroidectomy and animals 10 to 40 days following daily oral administration of 500 mg/kg of desiccated thyroid. The effects of hyperthyroidism and hypothyroidism on the heart were determined

cardiographically by the tachycardia and the bradycardia and confirmed on autopsy by the increase and the decrease of heart weight

Electrocardiographic changes of rats, dogs and monkeys receiving toxic doses of plasmochin and the acid-labile phosphate content of the rat's myocardium GRAHAM CHEN, E M K GEILING and J RILLA *Dept of Pharmacology, The Univ of Chicago* Electrocardiographically plasmochin has been found to produce a prolongation of the Q-T interval without bradycardia, an increase of the amplitude and occasionally an inversion of the T-wave in rats, dogs and monkeys receiving 5 mg/kg of the drug twice daily by stomach tube over a period from one to three weeks. During the later stage of intoxication, bradycardia also occurs. These changes are not permanent disappearing when the animal recovers after withdrawal of the drug. Such electrocardiographic abnormalities are not observed in animals in acute intoxication even after a lethal dose of plasmochin.

Coinciding with the electrocardiographic changes, it was found that in the myocardium of rats there was an increase of the acid-labile phosphate, as determined by the method for adenosine triphosphate (2.44 ± 0.28 for plasmochin treated, 1.64 ± 0.22 for normal rats).

In view of our findings of the stimulative effect of A T P on the isolated heart, whose activity has previously been depressed by plasmochin, this increase of the acid-labile phosphate (A T P most likely) may be interpreted as a compensatory mechanism in counteracting the effect of plasmochin [*Work done under contract with the Office of Scientific Research and Development*].

The joint toxicity of atabrine and quinine, atabrine and plasmochin, quinine and plasmochin GRAHAM CHEN and E M K GEILING *Dept of Pharmacology, The Univ of Chicago* The lethal toxicities of atabrine and quinine, atabrine and plasmochin, quinine and plasmochin were investigated by intraperitoneal injection in mice. It was found that the three combinations of these anti-malarials are different in their joint toxicity.

- (1) Atabrine and quinine act independently and similarly
- (2) Atabrine and plasmochin act independently but diversely
- (3) Plasmochin and quinine are synergistic in their joint action. These effects satisfy the criteria laid down by Bliss in respect to the toxicity of poisons administered jointly (Annals of App Biol 1939, Vol 26, 585).

[*Work done under contract with the Office of Scientific Research and Development*].

The effect of adenosine-triphosphate on the isolated heart GRAHAM CHEN, F SCHUELER, and E M K GEILING *Dept of Pharmacology, The Univ of Chicago* Adenosine-triphosphate (A T P) produces an increase of the coronary flow and an

increase of the amplitude, but no effect on the rate of contraction in an isolated heart preparation. However, in a normal contracting heart, A T P will only slightly increase the amplitude of contraction. It is effective after intocostin and following posterior-pituitary extract which causes marked coronary constriction.

By fortifying a heart with A T P it will recover much sooner to its normal physiological activity after depression by quinidine, plasmochin, acetylcholine or potassium. When the cardiac function has been severely impaired by quinidine or plasmochin, A T P will then restore the strength but not the rate of contraction.

A heart weakened through fibrillation by toxic doses of epinephrine, can be made to resume its normal rhythmicity and contractility by A T P. A T P will also increase the diastolic interval of a heart under the influence of digitalis. However, the relaxing effect of A T P is only temporary in a digitalized heart which has reached the stage of systolic arrest.

A T P differs from other cardiac stimulants in that it augments both the intensity and the capacity of cardiac contraction, principally the latter, the mechanism of its action probably lies in the enzymatic reaction between A T P and myosin, which liberates the chemical energy necessary for muscular activity by the rupture of the energy-rich phosphate bond of A T P.

Antithyroid activity of 24 compounds K K CHEN, PAUL N HARRIS, and ROBERT C ANDERSON (by invitation) *Lilly Research Labs, Indianapolis* Assays were carried out in rats by Astwood's method (J Pharmacol & Exper Therap 78 79, 1913) with 24 organic compounds. A control test was made simultaneously with thiouracil. The results follow.

	Effective concentration per cent
Thiouracil	0.001
Sodium salt of 4 methyl thiouracil	0.001
Diethyl thiobarbituric acid	0.001
4 Methyl-5-ethyl thiouracil	0.001
Thiouracil-4 acetic acid	0.002
Ethylene thiourea	0.005
Ethyl ester of thiourea-4 acetic acid	0.005
3 3 Dimethylallyl-ethyl thiobarbituric acid	0.01
Sodium salt of 4 phenyl thiouracil	0.02
2 Mercaptobenzimidazole	0.02
2 Mercaptothiazoline	0.05
1 Methylbutyl acetyl thiourea	0.1
Sodium salt of 4 amino thiouracil	0.1
β Methylallyl-ethyl thiobarbituric acid	0.2
Di n propyl thiobarbituric acid	0.2
Thioimidazolodione 2	0.2
n Butyl 1 methylallyl thiobarbituric acid	0.5
5-(1 Methylbutyl) 2 (β methylallyl) thiobarbituric acid	0.5
3 3 Dimethylallyl-ethyl barbituric acid	0.5
1 3 Dimethylbutyl-ethyl barbituric acid	0.5
Dimethyl barbituric acid	1.0
Sodium salt of 4 6-diamino 2 thiopyrimidine	1.0
Pseudothiohydantoin	1.0
1-Methylallyl isobutyl thiobarbituric acid	1.0

5-Ethyl pseudothiohydantoin was inactive at the 1 per cent level. The data on 4-methyl thiouracil and diethyl thio-barbituric acid are in general agreement with those of Chapman (Quart J Pharm 17 314, 1944) and Astwood (Endocrinology 36 72, 1945).

Pharmacology of fluoroacetate MAYNARD B. CHENOWETH and ALFRED GILMAN *Pharmacology Section, Medical Division, Chemical Warfare Service, Edgewood Arsenal, Md.* Fluoroacetic acid (sodium salt, "1080") is a valuable rodenticide (Science 102 232, 1945), pharmacologically unrelated to other halogenated acetates. Species variation in response to FA is extreme. Action of FA is exerted on the heart and CNS. Ventricular arrhythmias, marked ventricular alternation, myocardial depression and ventricular fibrillation follow FA administration in rabbits, goats, horses, rhesus and spider monkeys. Convulsions always occur without parallel cardiac abnormalities in the dog and guinea pig. EEG of the dog under FA is characteristic of *petit mal*. The cat, pig, rat, hamster and rhesus monkey manifest both cardiac and CNS responses to FA, but while the monkey always succumbs to the cardiac action, the others may succumb to respiratory depression or ventricular fibrillation.

LD₅₀ of methyl FA by any route is: dog, 0.06; rabbit, 0.22; guinea pig, 0.35; pig, 0.40; cat, 0.5; goat, 0.6; horse, 0.5-1.75; hamster, 2.5-5.0; rhesus monkey, 4.0; rat, 5.0; spider monkey, 14.0 mg/kg.

Isolated rabbit and rhesus monkey hearts develop characteristic abnormalities after FA poisoning, the rabbit at 0.0001 M and the monkey at 0.001 M FA. Marked protection against 0.01 M FA on rabbit and monkey hearts is obtained by substitution of 0.007 M acetate or pyruvate for glucose in the perfusate. Analyses of perfusate after poisoning reveal that considerable amounts of acetate appear when glucose substrate is provided. Lactate, pyruvate and total keto acid levels are not affected. This agrees with data obtained earlier by Barron on other systems (personal communication).

The irritability of the human uterus as affected by various drugs. GEORGE P. CHILD (by invitation), R. A. WOODBURY, RICHARD TORPIN (by invitation), WALTER G. WATSON (by invitation) and LOUISE JARBOE (by invitation) *Depts of Pharmacology and Obstetrics and Gynecology, Univ of Georgia School of Medicine, Augusta*. Human uterine and cervical pressures and electrouterograms were recorded simultaneously by the methods described elsewhere in these abstracts (see Woodbury et al.). Dysmenorrhea patients were very sensitive to pitressin, 0.2 vasopressor unit of pitressin having a greater oxytocic activity than 0.2 oxytocic unit of pitocin. These patients were also very sensitive to uterine distention. Some patients could tolerate a uterine distention of only 2 cc.

The spontaneous activity and the response to pitressin and distention were recorded before and after the administration of various sympathomimetic drugs, parasympatholytic drugs, magnesium salts, calcium salts, barbiturates, quimidine and opiates.

Uterine irritability was reduced by ephedrine, slow injection of epinephrine, beta-diethylaminoethyl phenyl-alpha-thienylglycolate hydrochloride (Stearns 600), beta-diethylaminoethyl phenyl-alpha-thienylacetate hydrochloride (Stearns 606), magnesium sulfate intravenously, and morphine. In some patients calcium salts and pitocin reduced uterine pain by converting disorganized uterine activity into organized contractions. In other patients some of the drugs had a more pronounced effect in reducing the pain without any marked alteration of the contraction pattern. [Financial grant from Frederick Stearns and Company supported these studies.]

Prothrombinopenic activity of the salicylates and pharmacologically related drugs BYRON B. CLARK and MIRIAM SPITALNY (by invitation) *Dept of Physiology and Pharmacology, Albany Medical College, Union Univ, Albany, N Y*. Several investigators have reported that the salicylates may cause a decrease in plasma prothrombin activity. This has been confirmed in animals, and further experiments have revealed several factors which augment this action. It has been demonstrated also that other pharmacologically related drugs have a prothrombinopenic action. Prothrombin clotting time was determined by a modified Quick procedure using 20 per cent plasma. The rat was found to be considerably more susceptible than the rabbit while the dog was quite resistant, therefore, the rat has been used chiefly. An assay of sodium salicylate, acetylsalicylic acid, and methyl salicylate on rats revealed that equal millimolar doses had about the same order of activity, although in some individual cases acetylsalicylic acid was considerably more active. The same was true in rabbits except that methyl salicylate was less active.

The prothrombinopenic action of sodium salicylate is greatly augmented by experimental hyperthermia induced either by yeast injections, or exposure to high environmental temperatures, and by hyperthyroidism. The data indicate that increased metabolism whether associated with fever or not increases the prothrombinopenic effect of sodium salicylate. When alcohol and sodium salicylate are administered daily for three days, the reduction in prothrombin activity is considerably greater than that caused by alcohol or salicylate alone.

In addition to the three salicylates examined, all of the following analgesic antipyretic drugs have been found to have prothrombinopenic activity: antipyrine, aminopyrine, acetanilid, acetophenet-

idin, and cinchophen. A similar action has been reported for quinine (J A M A 128 1093, 1915).

The effects of di-isopropyl fluorophosphate upon normal subjects and patients with myasthenia gravis. JULIUS H. COMBOL, JR., JOHN TODD (by invitation), GEORGE GAMMON (by invitation), GEORGE B. KOEHLER (by invitation) and ALFRED GILMAN. *Depts. of Pharmacology and Neurology, Univ. of Pennsylvania School of Medicine, Philadelphia, and Medical Research Lab., Edgewood Arsenal*.¹ Administration of di-isopropyl fluorophosphate (DFP) in oil to twenty-two human subjects (0.7 to 30 mg intramuscularly or 2.5 to 100 mg orally) resulted in marked reduction in plasma cholinesterase activity and slight decrease in red cell ChE activity. Plasma ChE did not return to normal for several days or weeks, restoration of red cell ChE required longer periods. Single intramuscular injections of DFP in oil (2 mg) had no consistent effects upon pulse rate, systolic or diastolic blood pressure, ECG, ballistocardiogram, vital capacity, or blood sugar in 7 normal subjects. Repeated injections produced no changes in hepatic, renal or hematopoietic function. The most frequent undesired effects were gastrointestinal.

Seven patients with myasthenia gravis were treated with DFP (2.5 to 210 mg over periods of 1 to 150 days). The effectiveness of DFP was compared with that of neostigmine by a series of objective dynamic and static muscle function tests and by electromyograms. DFP relieved the weakness of these patients for longer periods than did neostigmine but never to the same degree. In these patients, plasma ChE was reduced to 0-10% by DFP with only partial improvement in muscle power while neostigmine produced marked increase in power with decreases in plasma ChE to only 50-70% of normal. Efficacy of drugs in the treatment of myasthenia gravis cannot be determined by their effects upon plasma ChE.

A simple method of recording uterine motility in vivo. BRADFORD N. CRAVER (by invitation), PATRICIA SEIP (by invitation), ANNE CAMERON (by invitation), introduced by Frederick F. Yonkman. *Dept. of Pharmacology, Research Division, Ciba Pharmaceutical Products, Inc., Summit, N. J.* A uterine horn of a rabbit or cat can be exposed by an abdominal incision paralleling the course of the horn as the anesthetized animal is kept supine. The horn is brought out through the incision. Two short, superficial sutures are so placed in the longitudinal axis of the horn, 180° in the transverse circumference from the point of suspension in the broad ligament, that they are equidistant from their respective ends of the horn and include be-

tween them approximately half of the free length of the horn. These sutures are then used to anchor the horn to the abdominal musculature on opposite sides of the incision. A thread is then looped under the midpoint of the portion of the horn included between the two anchoring sutures. The thread is then pulled up through a small, inverted funnel, fitted with a short stem of comparatively large diameter, and fastened to a recording lever, the funnel serves as a moist chamber. In such a preparation the blood pressure and respiratory movements may be simultaneously recorded. This preparation permits repeated studies of uterine motility in the same animal if sepsis be maintained and a week to ten days be allowed for healing, but if a carotid cannula be used for recording blood pressure, only two experiments are feasible. The actions of pituitrin, and various salts of epinephrine, histamine, pyribenzamine, prisol (benzylimidazoline), trasentine and atropine in such a preparation are reported.

Nerve conduction in the absence of cholinesterase activity induced by di-isopropyl fluorophosphate (DFP). FREDERICK CRESCITELLI (by invitation), GEORGE B. KOEHLER (by invitation) and ALFRED GILMAN. *Pharmacology Section, Medical Division, Chemical Warfare Service, Edgewood Arsenal, Md.* Using isolated cat and frog nerves, the action potentials of the A fibers were recorded before and after local application of the irreversible anticholinesterase di-isopropyl fluorophosphate (DFP). DFP, like eserine base, in a 0.02 M concentration, blocked nerve impulses in 30-40 minutes enough to cause a 70-95 per cent decrease in the height of the action potentials beyond the region of application. The portion of the nerve proximal to the block conducted normally. Eserine salicylate (0.02 M) in two hours caused no change. The eserine or DFP block was abolished by washing the nerve with Ringer solution. In the case of DFP, merely lifting the nerve out of contact with the drug abolished the block.

These experiments indicated that the blocking action of DFP is not through its action as an anticholinesterase. To test this, into each of 12 bullfrogs were injected 2 grams/kg of DFP into the ventral lymph sac. Another 12 frogs served as controls. The action potentials of the 24 control sciatic nerves and the 24 experimental nerves showed no significant differences, either to single shocks or to repetitive shocks up to 43 per second applied for 10 minutes. The cholinesterase activity of the experimental sciatic nerves, however, was found to be 23 per cent of that in the control nerves. This figure is well within the limits of the standard error for the cholinesterase determinations. It is concluded that nerve fibers can conduct impulses under the condition of essentially complete absence of cholinesterase activity.

¹ Done under contract with Medical Division, Chemical Warfare Service.

Comparison of a chemical and a biological method for the assay of a purified digitalis preparation HELEN J DANOW (by invitation), DONALD R MATHILSON (by invitation), HARRY W HAYS (by invitation), (introduced by E Oppenheimer) *Dept of Pharmacology, Research Division, Ciba Pharmaceutical Products, Inc., Summit, N J* Digifolin, a purified extract of digitalis leaf, was assayed both chemically by the method of Bell and Krantz (*J Pharm Exp Ther* 83 213, 1945) and biologically by the USP XII cat method A tincture prepared from the USP Reference Standard Powder was used as the standard in both cases The results are summarized in the following table

Sample	U.S.P Units/cc Biologic Method	U.S.P Units/cc Chemical Method	Chem. potency Biol. potency $\times 100$
A	0.41	0.28	63.4
B	0.46	0.31	67.4
C	0.46	0.35	76.1
D	0.47	0.33	70.2
E	0.41	0.31	75.6
F	0.46	0.31	67.4
G	0.88	0.60	69.8
H	0.89	0.61	68.6
I	1.01	0.59	59.0
J	50	32.8	65.6
K	50	32.0	64.0
L	40	25.5	63.0

Av 67.6

The average chemical potency of the samples assayed was approximately 70% of the biological potency This discrepancy between the two methods indicates that the determination of the unsaturated lactone groups is not necessarily a measure of the biological potency

This data would indicate that the chemical method may be used as a supplement to, but not a substitute for, the biological method

The anemia produced by paraphenylenediamine in dogs JOHN EMERSON DAVIS *Dept of Pharmacology, Univ of Arkansas, Little Rock* Six dogs were injected subcutaneously with paraphenylenediamine dihydrochloride (30 mg per kgm) Within a few hours, all dogs showed some form of apparently localized edema The edema manifested itself in the face of one dog, in the throat and neck of a second, and in 3 of the feet of a third dog In the other 3 dogs, the eyelids became very edematous, being swollen shut in 2 of the animals All dogs ultimately showed marked hyperemia and signs of irritation of the tissues around the eyes, which persisted for several days One dog lost much secretion through the mouth, and died on the fifth day after injection

Four of the dogs developed significant anemia within 48 hours following medication with para-

phenylene diamine In one dog, the erythrocyte number returned to normal within 5 days, but in 2 animals, the anemia persisted, and even progressed, through the sixth day following medication Normal erythrocyte counts were reduced in the 4 dogs by 23, 37, 44, and 54 per cent respectively Hemoglobin percentages were also reduced, but not so greatly, perhaps because of an active, acute hemolytic process Icteric indices, in 2 dogs, were elevated to values of 40.1 and 42.2 on the fourth day after medication The anemia produced by paraphenylenediamine, in these experiments, appears to be a hemolytic anemia The problem is still under investigation

A statistical examination of the sources of error in the assay of mydriatic drugs by means of the rabbit's pupil EDWIN J DE BEER *The Wellcome Research Labs., Tuclahoe 7, N Y* Statistical methods were employed to determine the practicability of using the increase in pupil diameter of the albino rabbit's eye as caused by mydriatic substances as an assay method for this type of drugs A Latin square experimental design was used and the results were subjected to an analysis of variance It was found that the curve relating the gain in pupil diameter was essentially a linear function of the log of the concentration Other types of curvature were not significant This is favorable for the setting up of a practical biological assay The experimental design used permits the segregation and estimation of the variation due to the difference between animals This was found to be relatively large On the other hand, the variation introduced by repeated use of the same animals was not significant This indicates that neither increased sensitivity nor tolerance was developed and that the experimental designs to be used for the assay should favor the repeated use of the same animals Typical assays were carried out and estimates of precision based on the ratio of the standard deviation to the slope of the log concentration response curve have been obtained

The carcinogenic activity of 2-acetaminofluorene Effects of concentration and duration of exposure FLOYD DEEDS and ROBERT H WILSON *Pharmacology Division, Bureau of Agricultural and Industrial Chemistry, U S Dept of Agriculture* Wilson, DeEds, and Cox (*Cancer Research*, vol 1, Page 595, 1941) have shown that all rats receiving diets containing 0.031, 0.062, and 0.125 per cent of 2 acetaminofluorene (AAF) developed tumors if they lived long enough It has now been demonstrated that all rats eating diets containing 0.016 and 0.008 per cent AAF, and that five out of six rats on a 0.004 per cent level developed tumors, but that none of the five rats receiving the 0.001 per cent diet showed effects that could unquestionably be attributed to AAF Decrease in

concentration increased the latent period for tumor development

The effect of duration of exposure to AAF was determined by placing groups of rats on diets containing AAF for varying periods. The initial concentration of AAF was 0.125 per cent, but due to the poor condition of those animals still on the experimental diet the concentration was lowered to 0.031 per cent after 51 days. All rats receiving AAF for 75 days or more developed macroscopic tumors. All rats receiving AAF for 50 days showed fewer, but typical macroscopic or microscopic lesions. In the 25-day rats the lesions were minimal, but there was nevertheless a definite carcinogenic effect. Decrease of exposure time increased the latent period for tumor development.

Failure of o- or p-mononitrophenol to produce cataract. W. C. DIETRICH (by invitation) and R. BEUTNER, *Dept. of Pharmacology, The Hahnemann Medical College and Hospital of Philadelphia* (Read by title). The production of cataract by α -dinitrophenol in human beings after prolonged use can be reproduced in very young chicks in a few hours (B. H. Robbins, 1944). By this method o- and p-nitrophenol were studied and found to be devoid of that specific toxicity for lens tissue which characterizes the dinitro compound. The experiments were performed on 7 days old chicks, kept for 6 days previously under uniform and controlled conditions, 3 groups, of 28 chicks each, were fed daily 20 grams of a commercial brand of chick food with 50 mg of the respective nitrophenol added (0.25%). The chicks fed with α -dinitrophenol developed a marked opacity of the anterior portion of the lens within 24 to 48 hours. Four days later the opacity receded to the posterior portion of the lens. Chicks on the o- or the p-nitrophenol diet did not show this peculiar opacity at all. Chicks on a control diet without any nitrophenol gained 86% in 3 weeks. The chicks on the o-nitrophenol diet gained an average of 101% in 3 weeks, those on the p-nitrophenol gained 98%, but those on α -dinitrophenol only 31%! The latter group also showed a 1 to 4 degree F. higher cloacal temperature than either the drugless controls or the o- and p-nitrophenol fed chicks.

The absorption, distribution and elimination of different pharmaceutical forms of sulphadiazine. R. W. DINGWELL (by invitation) and E. M. BOYD, *Dept. of Pharmacology, Queen's Univ., Kingston, Canada*. Four grams of sulphadiazine were given orally to human volunteers in the form of tablets or an emulsion or an emulsion of microcrystals or an emulsion containing sodium lactate or an emulsion containing potassium lactate. At intervals of 0.5, 1, 2, 4 and 6 hours after taking the drug, samples of blood and urine were collected. Whole blood and plasma were analyzed for free and combined sulphadiazine. Likewise and uncentrifuged and

centrifuged urine were similarly analyzed and the total volume of urine noted. The urinary sediment was viewed microscopically for signs of renal damage and a clinical record of the subject was kept. At the time of writing this abstract, in sufficient data were available to permit of definite conclusions. The indications are that some pharmaceutical forms of sulphadiazine, especially the emulsions, are absorbed more rapidly than are the table forms and there is evidence that a higher and more prolonged blood level is reached. There were also differences in urinary excretions which will be described.

Toxicity and primary irritation of some chemical compounds following oral administration and skin application. JOHN H. DRAIZE, ELSIE ALVAREZ (by invitation) and MARIE F. WHITSELL (by invitation), *Division of Pharmacology, Food and Drug Administration, Federal Security Agency, Washington, D. C.* In the course of work on projects connected with the war effort, data on toxicity and primary irritation following topical skin application was obtained for numerous chemical compounds.

The toxicity studies were conducted in the rabbit with intact and abraded skin following single (acute) or repeated daily (subacute) applications for varying periods of time (maximum of three months). In most cases the oral toxicity of the compound was determined concurrently. Conclusion: It is impossible to predict toxicity by skin application from oral data and vice versa.

Data on primary irritation to skin was obtained for several thousand compounds submitted as prospective insect repellent candidates. Compounds of similar chemical structure have a tendency to exhibit similar degrees of irritancy, however there were sufficient exceptions to warrant the conclusion that it is impossible to predict potential skin irritation solely on the basis of chemical structure. [A portion of the funds used in this investigation was supplied by a transfer, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Division of Pharmacology of the Food and Drug Administration.]

Biochemical studies on the toxicology of alpha-naphthylthiourea (ANTU). K. P. DuBois (introduced by E. M. K. Geiling), *Univ. of Chicago Toxicity Lab.* Pleural effusion and edema characteristically follow poisoning with the rodenticide ANTU (Richter—J. Am. Med. Assoc. 129:927, 1945). Marked carbohydrate disturbances have also been observed in rats and dogs (DuBois, Holm, Doyle—in press). The administration of insulin or adrenal cortical extract decreases the extent of the blood sugar changes. Investigation of the glycolytic and respiratory enzymes of lung tissue indicates a relationship between carbohydrate disturbance and lung damage. Lungs from rats poisoned with

ANTU show marked reduction in cytochrome oxidase and succinic dehydrogenase. These findings are related to the effects of thiourea as used in the treatment of hyperthyroidism.

The effects of body-gassing with mustard vapor on the carbohydrate metabolism of dogs A J DZIEMIAN (introduced by Paul Dumke) *The Clinical Research Section, Medical Division, Chemical Welfare Service, Edgewood Arsenal, Maryland*. Body gassing of dogs with mustard gas vapor caused a moderate hyperglycemia during the first two days after gassing, followed by a decrease to normal or hypoglycemic values by the fifth or sixth day after mustard. The dogs may show a profound hypoglycemia shortly before death.

Oral glucose tolerance curves are flatter than normal and have a plateau type shape. Intravenous glucose tolerance tests on gassed dogs show a faster rate of disappearance of added glucose from the blood, which may in part account for the apparent increased oral tolerance. The latter may also be partly caused by decreased intestinal absorption. Neither the stomach emptying time nor the intestinal motility are changed after mustard.

The increased intravenous tolerance is not caused by any decrease in the kidney tubular re-absorptive capacity, although an increased glomerular filtration rate and glucose clearance may account for some of the increased glucose loss. Simultaneous arterial and venous intravenous glucose tolerance tests show that, in the head at least, there is no increase glucose utilization by the tissues after mustard.

A number of the effects described above are similar to those found after thermal burns.

2,3-Dithiolpropanol ("BAL") as a specific detoxifying agent for arsenic HARRI EAGLE, HAROLD J MAGNUSON and RALPH FLEISCHMAN (introduced by E K Marshall) *Venerical Disease Research Laboratory of the U S Public Health Service, Johns Hopkins Hospital, Baltimore, Maryland*. 1 2,3 Dithiolpropanol ("BAL") injected subcutaneously, intramuscularly, or intravenously in aqueous or propylene glycol solution, proved effective in the treatment of acute and subacute mapharsen poisoning in rabbits.

2 The antidotal action of BAL was referable to its ability to remove the arsenical from its combination with cells, with the excretion of the stable and relatively non toxic thioarsenite so formed. Trypanosomes rapidly immobilized and apparently killed by arsenicals were resuscitated on the addition of BAL, due to the removal of the bound arsenic from the cell. Similarly, in rabbits injected with mapharsen, Lewisite or phenyl arsenoxide, the administration of BAL caused a striking increase in the rate of urinary arsenic excretion, in some cases exceeding a hundred fold.

3 Although BAL was unstable in aqueous or

propylene glycol solution, solutions in peanut oil could be sterilized by heat with only slight loss in activity. With the addition of 2 grams of benzyl benzoate for each gram of BAL, the latter was miscible with peanut oil in all proportions.

4 Such solutions in peanut oil and benzyl benzoate injected intramuscularly proved effective in the treatment of mapharsen, Lewisite and phenyl arsenoxide poisoning in rabbits.

5 The widest margin of safety between the effective and toxic levels of BAL so administered was provided by a schedule involving four injections at four-hour intervals, followed in some cases by daily injections for six days. On this schedule, individual doses of 1 to 10 mg per kg BAL saved more than half the animals injected with lethal doses of mapharsen, Lewisite or phenyl arsenoxide. Since the maximum tolerated dose of BAL so injected was 35 mg per kg, the margin of safety provided was sufficiently large to indicate the feasibility of its human use.

6 This has been confirmed in more than 200 human cases of arsenic poisoning treated to date.

Cinchona alkaloids 5 Physiological disposition of cinchonine metabolic products in man DAVID P EARLE, JR (introduced by James A Shannon) *Research Service, Third Medical Division, Goldwater Memorial Hospital, and the Dept of Medicine, New York Univ College of Medicine, New York*. When cinchonine is administered, recovery from urine of cinchonine and isolatable metabolic products accounts for approximately 85% of the dose. Five per cent is recovered as cinchonine, 55% as carbostyryl, and 25% as the second metabolic product. When the carbostyryl is administered, 35% is recoverable as such as well as sizable amounts of the second metabolic product, the latter contains an additional oxygen on the quinuchidine nucleus.

Absorption of cinchonine and its carbostyryl (first metabolic product) is essentially complete. Plasma protein binding of the carbostyryl is 52% at 2 mg of drug per liter and 4 grams albumin per 100 ml plasma, as compared with 60% for cinchonine. The renal clearance of the carbostyryl approximates that of renal plasma flow and is unaffected by alkali administration. The maximal clearance of cinchonine is one third that of the carbostyryl and may be reduced to one sixth by alkali administration. Plasma levels achieved by the carbostyryl are higher than those achieved by cinchonine (15 times higher at 0.5 gram daily to 3 times at 3 grams daily), whether cinchonine itself or the carbostyryl is administered. Since plasma cinchonine levels are very low for a drug not extensively localized, the initial step in the metabolism of cinchonine is rapid. Metabolism to the second product proceeds at a slower rate. [Based upon work done under a contract recommended by

the Committee on Medical Research, between the Office of Scientific Research and Development and New York Univ]

Pamaquin 3 Occurrence of hemolytic anemias DAVID P EARLE, JR (by invitation), PERLIN KNOWLTON (by invitation), ROBERT W BERNIER (by invitation), JOHN V TAGGART (by invitation), CHARLES G ZUBROD (by invitation), WILLIAM J WELCH (by invitation), and JAMES A SHANNON. *Research Service, Third Medical Division, Goldwater Memorial Hospital, and the Dept of Medicine, New York Univ College of Medicine, New York* (Read by title) The toxicity of pamaquin involves the gastro-intestinal tract, the central nervous system and the elements of the blood. Of these, acute hemolytic anemia is the most serious hazard.

Pamaquin has been administered under close clinical supervision to 167 patients for from 3 to 14 days in daily doses varying from 4 to 90 mg of the base. An acute hemolytic anemia occurred suddenly after 3 to 5 days of therapy in 6 patients, and developed slowly in 1 patient after 7 days. Recovery was invariably prompt upon withdrawal of drug, although transfusions were deemed necessary in 3 instances. No hemolytic anemias occurred among 20 patients given less than 20 mg a day. The 6 acute anemias occurred among 74 non-white patients receiving 30 mg or more per day (1 received 90 mg). Gradual hemolytic anemia occurred once among 73 white patients given 30 mg or more per day (20 received 90 mg daily). There was no relation between the incidence of anemia and the plasma drug level nor the presence of malaria or fever. Special studies were made in 23 patients receiving pamaquin, 1 of whom developed acute hemolytic anemia. None of the following factors could be demonstrated to have a causal relation to hemolytic anemia: isagglutinins, isohemolysins, autoagglutinins, cold agglutinins, methemoglobinemia, and resistance of erythrocytes to hypotonic saline and to mechanical trauma. [Based upon work done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and New York Univ]

The effect of certain new antihistamine drugs on bronchial spasm FRED W ELLIS and JAMES F NEWSOME (by invitation). *Dept of Pharmacology, Univ of North Carolina, Chapel Hill, N C*. Observations of the antihistamine effect on isolated perfused guinea pig lungs was made on the following compounds: S-82 (β -isopropylaminoethyl benzhydryl ether HCl), S-150 (N-(p-tertiary-octylphenoxyethoxyethyl) morpholine HCl), S-154 (β -benzhydryloxyethyltrimethylammonium p-toluenesulfonate), S-157 (4- β -benzhydryloxyethyl-4-methyl-morpholinium p-toluenesulfonate), S-158 (β -benzhydryloxyethyl dimethylethylam-

monium p-toluenesulfonate), S 161 (β -benzhydryloxyethyl-hydroxyethyl methylamine HCl), S 161 (N- β hydroxypropylephedrine methiodide) and S 166 (N- β hydroxypropylephedrine). Bronchial spasm was induced by 0.1 milligram of histamine. Upon recovery, antagonism to histamine was determined by injecting simultaneously into the perfusion fluid the same dose of histamine and 10 milligrams of the S compound. S 82 was the most potent drug in this group. Usually, it completely prevented histamine spasm and, frequently, produced a superimposed dilatation. S 158 and S 151 were not as consistent and powerful as S 82. S 157 and S 161 were partially effective, and S 150 was almost completely ineffective in antihistamine activity. S-164 and S 166 failed to show any degree of antagonism to histamine.

On intact dog lungs, Jackson's method was used to study the broncho dilator activity of the following drugs: S 51 (β dimethylaminoethyl benzhydryl ether HCl), S 59 (β monomethylaminoethyl benzhydryl ether HCl) and S-82. The animals were either anesthetized with ether and pithed or anesthetized with pentobarbital and respiration was paralyzed with dihydro-beta-erythroidine. Histamine was injected intravenously in doses of 0.1 to 0.3 milligram per kilogram and when the maximum effect occurred, 3.0 to 6.0 milligrams per kilogram of the S-compound were injected intravenously. S 51 exerted the most marked antagonism to bronchial constriction and S-59 and S 82, while showing a variable effectiveness, were of less potency in relieving the induced spasm.

Effects of a bone marrow-spleen immune serum on the blood picture of mice G A EMERSON, P L EWING and THURLO B THOMAS (by invitation). *The Univ of Texas Medical Branch, Galveston*. Preliminary to chemotherapeutic study of Bogomolov's serum ("ACS", antireticular cytotoxic serum, "REIS", reticuloendothelial immune serum), we have studied effects of an immune serum, prepared by repeated injection of mouse spleen and bone marrow in rabbits, on the blood picture of normal mice, splenectomized mice, and mice subjected to laparotomy as a sham operation. The complement-fixation titers of 2 sera were 1:80 and 1:1280, the stronger serum was used in most of the experiments in doses of 0.02-5.0 ml/kg given intraperitoneally. No precipitin test could be elicited with various forms of the antigen in either serum. Both were moderately anticomplementary. Blood was examined for total red and white cell counts, reticulocytes, small and large lymphocytes, polymorphonuclears, monocytes, eosinophils, "basophils", and stab cells, after single and repeated injections of the sera. No constant effects were noted with lower doses, at higher doses which affect the white picture moderately, a

severe macrocytic anemia with showers of reticulocytes was noted. This was most marked in splenectomized mice. Danger of a severe hemolytic anemia should be considered in the therapeutic use of so called blocking doses of ACS.

A comparison of the effects of streptomycin in the nutrition of the rat and the mouse. EMERSON, GLADYS A. and SMITH, D. G. (introduced by Hans Molitor) *Merck Inst for Therapeutic Research, Rahway, N. J.* Weanling rats and mice were maintained on purified diets containing 2500 units of streptomycin per gram of ration. Rats so treated showed signs typical of those observed in experimental biotin deficiency. The administration of biotin resulted in resumption of growth and an alleviation of deficiency signs. The change in coliform count, a reduction followed by a return to normal, was similar to that seen with succinyl sulfathiazole, however, the degree of depression was far greater. Mice were reared on the streptomycin containing ration for a period in excess of three months. The growth rate was the same as for the controls receiving the purified diet alone. The animals appeared normal in all respects, furthermore, the addition of dried liver to the ration did not further augment growth. Streptomycin was without effect upon the total bacterial or coliform counts of the feces. However, mice receiving a stock ration containing streptomycin showed a sustained reduction in intestinal microorganisms.

Growth requirements of *Endameba histolytica*. GLADYS A. EMERSON and EDER LINDSAY HANSEN (introduced by Hamilton H. Anderson) ¹ *Division of Pharmacology and Experimental Therapeutics, Univ of California Medical School, San Francisco*. *E. histolytica* and organism "t" have been cultured in purified or semi-purified media of varying composition. Amino acid nitrogen was provided by Difco proteose peptone, an acid hydrolysate of casein, or by mixtures of amino acids. Nitrogenous bases, enzymatic digest of liver (Wilson, Fraction L) and all of the known vitamins were provided in some of the media. All cultures contained rice starch grains, cholesterol, buffered physiologic saline, cysteine and methionine. Maximum growth was obtained with media containing proteose peptone and the liver digest. Mixtures of 8 or 18 amino acids were inadequate for continued growth. The casein hydrolysate was toxic in concentrations in excess of 0.5%. An enzymatic digest of liver contained factor(s) (probably folic acid) necessary for the optimal growth of *E. histolytica*. Rice starch was not replaceable by other carbohydrates. Trace minerals were either nonessential or were present as contaminants.

Bacterium "t," associated with *E. histolytica*, grew in all media. [The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Univ of California.]

Effects of a bone marrow-spleen serum on *Trypanosoma equiperdum* infection in mice. P. L. EWING and G. A. EMERSON. *Univ of Texas Medical Branch, Galveston*. Involvement of the reticulo-endothelial system in trypanosome infections (Pfeiffer and Tatum, J. P. E. T., 53: 358, 1935) suggests that a stimulant of the RES might be curative. Normal and splenectomized white mice were given a standard inoculum of *Tr. equiperdum* before and after treatment with ACS, an immune serum prepared by repeated injection of mouse spleen and bone marrow in rabbits. Over a range of doses, there was no indication of a chemotherapeutic effect as measured by time of death. Since this infection is fulminant, it is possible that exogenous stimulation of the RES is only quantitatively ineffective. Further studies to test this possibility are being made with the relatively benign *Tr. lewisi* infection in rats. [Part of this study was completed at the Univ of Wisconsin, Madison, through the courteous cooperation of Prof. A. L. Tatum. We are grateful also to the Smith, Kline and French Laboratories, Philadelphia, for a grant-in-aid.]

The action of dimethylamino-ethanol upon the heart-lung preparation of the dog. A. FARAH (by invitation) and O. KRAYER. *Dept of Pharmacology, Harvard Medical School, Boston, Mass.* The erythropleum alkaloids are esters of the mono- and di-methylaminoethanols. It has been previously shown that these alkaloids have a positive inotropic action on the failing heart. Erythropleic acid, the acid component of the alkaloid erythropleine, has no demonstrable cardiotonic effect (Maling, H. M. and O. Kraye, J. Pharmacol. and Exper. Therap., in press).

We have studied the action of dimethylamino-ethanol on spontaneous and sodium pentobarbital failure in the H. L. P. of the dog. With doses of 70-150 mg. per liter of blood there is a positive inotropic effect characterized by a fall in pulmonary and right and left auricular pressure, a decrease in the diastolic volume of the heart, and an increase in the systemic and coronary flow. The heart rate is not changed by therapeutic doses, while toxic doses (800-1000 mg.) produce auriculoventricular dissociation. The fact that the therapeutic doses of dimethylaminoethanol do not increase the heart rate sharply differentiates its action from that of adrenaline like substances. Furthermore, the short latency period observed with dimethylaminoethanol differentiates the action of this substance from that of the cardiac glycosides.

Moe and Kraye (J. Pharmacol. and Exper.

¹ We are indebted to the following individuals for materials used: M. S. Dunn, J. J. Eiler, D. M. and L. D. Greenberg, E. E. Howe, H. D. Lightbody, H. Molitor and E. L. R. Stokstad.

Therap 77 220, 1943) have shown that the alkalines of the veratrum alkaloids have a positive inotropic action on the failing heart, but are about 300 times less effective than the corresponding ester alkaloids. Dimethylaminoethanol is also about 200-300 times less effective than the erythrophleum ester alkaloids. We have tested the acetate, benzoate, and cinamate esters of dimethylaminoethanol but have not been able to demonstrate any potentiation of action over that of the alkaline.

The analgesic action of the racemates of I-amino-1-phthalidylpropane hydrochloride EDWIN J. FELLOWS *Temple Univ School of Medicine, Philadelphia*. Since I-amino-1-phthalidylpropane hydrochloride (I) contains two asymmetric carbon atoms, two racemic forms and four optical isomers are possible. In previous studies it was found that a mixture of the racemic forms of I, exhibited analgesic activity. During the course of subsequent experiments it was found that different samples of I, exhibited less analgesic activity than originally observed. It appeared possible that one of the racemates of I, might be more active than the other and that the discrepancies noted in the recent samples of I could be explained by a decrease in the amount of the more active racemate in the mixture. The present studies are concerned with detailed comparisons of the pure racemates of I in animals. In these experiments it was found that the high melting racemate (A) of I manifested greater analgesic activity in rats and cats than the low melting racemate (B). It also was found that the two racemates evidenced a qualitative difference in their action. Racemate A produced an action which suggested a mixture of stimulation and depression of the central nervous system whereas a depressant action on the nervous system appeared to be the outstanding effect of racemate B.

Glucuronic acid excretion after various glycols JEAN K. FELLOWS (by invitation) and F. P. LUDUEÑA *Dept of Pharmacology and Therapeutics, Stanford Univ School of Medicine, San Francisco 15, California*. Using Deichman's quantitative method (*J Lab Clin Med* 28 770, 1943) glucuronic acid excretion was determined for 2 to 3 days in urines of rabbits receiving large and small doses of diethylene glycol monoethyl ether ("Carbitol"), diethylene glycol, ethylene glycol, glycerol, and propylene glycol. Propylene glycol and "Carbitol" were administered gastrically and hypodermically, all others, gastrically. Significant increases in glucuronic acid excretion occurred only after propylene glycol (105 to 1185%) and "Carbitol" (22 to 875%). Our negative results with glycerol and ethylene glycol and positive results with propylene glycol confirm those of Neubauer (*Arch exp Path Pharm* 46 133, 1901) and Miura (*Biochem Ztschr* 36 25, 1911). Why "Carbitol," a member of the ethylene series, should differ from

the ethylene and diethylene glycols is not clear, but evidences from other studies in this department indicate that both "Carbitol" and propylene glycol are fairly readily disposed of in the body.

Production of cataracts in rats with beta tetralol O. GARTH FITZHUGH *Division of Pharmacology, Food and Drug Administration, Federal Security Agency, Washington, D. C.* In a study on the chronic toxicity of beta tetralol (1,2,3,4 tetrahydro beta naphthol) it was observed that this compound produced cataracts in rats in from 4 to 6 weeks. All rats on concentrations of 1 and 2 per cent beta tetralol in their diet developed cataracts. In rats on lower concentrations of the drug in the diet the time of development of the opacities was delayed. This experimental production of cataracts in the rat by a chemical may prove of value to ophthalmologists.

Data will be presented to show the relative toxicity of different levels of beta tetralol in the diet. Beta tetralol was under investigation because of its insect repellent properties. [A portion of the funds used in this investigation was supplied by a transfer, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Division of Pharmacology of the Food and Drug Administration.]

The effect of xanthines and pituitrin on water loss DOROTHY FULGHUM (by invitation) DOROTHY FITZWATER (by invitation) and O. S. GIBBS *Memphis, Tenn.* Rats starved 24 hours fed 5% body weight of water lose 94% renally in 5 hours, the remainder extra-renally provided the room temperature has not been or is over 80°F. Xanthines do not constantly change either figure but under hot conditions (90°F) may increase the extra-renal water loss. With water ingestion the results are harmless, as is the addition of sodium chloride in cool weather, but under hot conditions sudden death of the animals may take place. It is suggested that this is due to sodium chloride poisoning due to a disbalance resulting from uncontrolled extra-renal water loss. While the action of pituitrin is to decrease renal water loss materially, the body weight remains nearly constant with controls indicating a corresponding increase of extra-renal water loss. In spite of this large and constant water loss pituitrin injections do not appear as hazardous as large doses of caffeine presumably because of its powerful diuretic effect on chlorides. Sodium chloride poisoning in rats simulates one type of heat exhaustion and may be its fundamental cause. The use of pituitary extract in such conditions may be indicated.

The tissue distribution and the excretion of antimony after administration of tervalent and quinquevalent antimonials ALFRED GELLHORN (by invitation) and H. B. VAN DYKE *Dept of Pharmacology, College of Physicians and Surgeons,*

New York. The tissue localization and the excretion of the tervalent antimonials, tartar emetic and Anthiomaline, and the quinquevalent antimonials, Neostibosan and Stibranose, were studied in the hamster following single or multiple intraperitoneal injections. Striking differences were observed in the behavior of the compounds. For example, with the tervalent antimony compounds, 10-15 per cent of the injected antimony is localized in the liver, whereas with the pentavalent antimonials less than 5 per cent of the administered antimony can be recovered from the liver. Fifteen per cent of the injected tervalent antimony is excreted in the urine and 50 per cent is eliminated from the body by way of the gut, of the injected quinquevalent antimony, about 70 per cent is excreted by the kidneys and about 4 per cent is eliminated in the intestinal contents.

The relation of tissue concentration and distribution of antimony to toxicity and to chemotherapeutic effectiveness in experimental leishmaniasis will be discussed [Work done under contract with the Office of Scientific Research and Development].

The diuretic-antidiuretic actions of posterior pituitary and sodium chloride. O. S. GIBBS and DOROTHY FULGHUM (by invitation) Memphis, Tenn. Male Wistar rats under standardized conditions confirm that hypodermic pituitrin at the time of water feeding delays water excretion (40%) and increases sodium chloride output, (300-600%). Under such conditions pituitrin is a water anti-diuretic and the most powerful chloride diuretic known. By raising the total sodium chloride ingested the amount excreted, which does not exceed normal urinary concentrations, can be adjusted that the anti diuretic action on the water becomes reversed and a total diuresis results. According therefore to the available sodium chloride pituitrin can increase or decrease water excretion. The possibilities inherent in this dual action of pituitrin seem entirely neglected in renal therapeutics. As the effect of pituitrin is quantitatively greater on chlorides than water a bioassay method based on this function may be practical. The dual effect of pituitary offers comparison with other anti-diuretic (water) drugs. Morphine does not increase the chlorides in rats, and probably does not act via the pituitary mechanism.

94% of orally fed water is excreted renally in 5 hours. The addition of NaCl to this water firstly results in a marked water anti-diuresis reaching a peak around 1% salt concentration, but accompanied by a considerable salt increase. Further salt addition reverses the anti-diuretic effect. At 3% salt the renal water excretion may now exceed 100% of that administered. As this effect has not been produced by eq. mol. solutions of Li or KCl it is probably due to the sodium ion. Xanthines, espe-

cially caffeine, may potentiate either actions of pituitary according to existing conditions.

Comparison of cinchona alkaloids on the circus rate of the auricle in patients with auricular fibrillation. HARRY GOLD, WALTER MODELL, HAROLD L. OTTO (by invitation), and LAWRENCE W. HANLON (by invitation) [with the technical assistance of Jenny Oppenheim (by invitation)] Dept. of Pharmacology, Cornell Univ. Medical College, and Cardiac Services of the Beth Israel Hospital and Hospital for Joint Diseases, New York, N. Y. The effects of U.S.P. quinidine, synthetic quinidine, dihydroquinidine, and U.S.P. quinine on the circus movement of the auricles were compared in patients with auricular fibrillation. Subjects were at bed-rest and in most instances digitalized. Precordial electrocardiograms were taken before, and at 2 hour intervals after the oral administration of a dose. A sufficient number of F-F intervals were measured to obtain reliable average values. Each patient received 3 to 6 doses of one or more of the alkaloids, ranging between 0.1 and 2.0 grams. The maximum effect was present in 2 to 4 hours. Dosage-response curves of percentage slowing of the circus movement proved to be sigmoid in shape. The reports of comparisons of the cinchona alkaloids in the literature indicate that they possess quantitative differences in their action, with the implication that more of one than of another may be expected to produce similar effects. Previous investigators failed to establish the dosage-response curves for the various compounds. The present study shows that those comparisons were usually made in the range of dosage falling in the flat part of the curve. The present study shows that while the various cinchona alkaloids slow the circus movement in the auricle, and some are more potent than others, the ceiling effect differs, it is as much as twice as high for some as for others. The results, therefore, indicate that, whereas these compounds are interchangeable in therapeutics within certain ranges of action provided comparable doses are given, there are other ranges of action in which the drugs are not interchangeable, irrespective of the size of the dose.

Further studies on the anticonvulsant properties of tridione (3,5,5-trimethylloxazolidinedione). LOUIS S. GOODMAN, EWART A. SWINYARD¹ (by invitation), and JAMES E. P. TOMAN. Depts. of Pharmacology and Physiology, Univ. of Utah School of Medicine, Salt Lake City, Utah. Tridione was further studied in mice, rats, rabbits, cats and monkeys to attempt elucidation of its highly specific anticonvulsant action in the petit mal triad. Non-depressant doses elevated the metrazol seizure threshold in all species more than did barbiturates, and single doses showed residual effects for 48 hrs.

¹ Winthrop Research Fellow in Pharmacology

Thresholds for "petit mal" EEG dysrhythmias elicitable by subconvulsant doses of metrazol (rabbits, monkeys) were markedly elevated by tridione, moderately increased by phenobarbital and unaffected by diphenylhydantoin. The EEG and neurological effects of depressant doses of tridione were completely reversible by metrazol, barbiturate depression was not similarly reversible.

Tridione increased moderately the normal electroshock threshold in all species studied, in contrast to diphenylhydantoin which was ineffective (see accompanying abstract). Tridione elevated toward normal the metrazol and electroshock thresholds experimentally lowered in rats by cellular hydration due to acute extracellular electrolyte depletion (isomolar glucose, 1 p). Phenobarbital was equally effective and diphenylhydantoin less so. Tridione raised the threshold for nonconvulsive EEG responses to single cortical shocks (rabbits). The drug obliterated tonic extensor components of maximal electroshock seizures (rats, rabbits, cats), but its effective index for this action was lower than that of phenobarbital or diphenylhydantoin, and recovery from refractoriness and post-seizure depression was not as rapid as after diphenylhydantoin.

Tridione selectively depressed multineuronal transmission in the spinal cord (spinal cats) without primarily affecting two-neuronal transmission, but it was less effective than benzimidazole. Metrazol reversed the cord effects of tridione.

The above studies are continuing and other oxazolidine-dione derivatives are being examined [Aided by grants from the Research Fund, Univ of Utah School of Medicine and the Abbott Lab].

Studies on the anticonvulsant properties of diphenylhydantoin. LOUIS S. GOODMAN, EWART A. SWINYARD¹ (by invitation) and JAMES E. P. TOMAN, *Depts of Pharmacology and Physiology, Univ of Utah School of Medicine, Salt Lake City, Utah* (Read by title). Diphenylhydantoin specificity in grand mal and psychomotor epilepsy prompted reexamination of its anticonvulsant properties in mice, rats, rabbits, cats, and monkeys. Diphenylhydantoin fails (a) to increase metrazol seizure thresholds in all species, (b) to prevent "petit mal" EEG dysrhythmias elicitable in rabbits by subconvulsant metrazol doses, (c) to elevate normal electroshock threshold in all species (alternating or interrupted direct current and shocks of 0.1 to 10 sec), (d) to increase threshold for nonconvulsive EEG discharges in rabbits to single cortical shocks. Toxic doses actually lower metrazol and electroshock seizure thresholds cited above.

In contrast, diphenylhydantoin elevates electroshock seizure threshold (rats) lowered by cellular

hydration, although toxic doses synergize with hydration to cause convulsions. It also abolishes tonic extensor components of maximal electroshock seizures (rats, rabbits, cats) produced by brief supramaximal shocks. Even toxic doses which lower normal electroshock seizure threshold exhibit this action. Despite increased severity and duration of clonic components of maximal seizures, diphenylhydantoin accelerates recovery from refractoriness and post-seizure depression. Threshold for seizures produced by 10 sec stimulation is not raised by diphenylhydantoin but the convulsion (verifiable electroencephalographically) is so shortened as to terminate within the stimulation period, and may be overlooked.

Diphenylhydantoin does not significantly modify the resting EEG, but toxic doses produce evidence of excitation. Also, after diphenylhydantoin, the EEG during maximal seizures exhibits reduction in voltage and frequency of surface negative spike discharges, despite the apparent severity of the overt clonic seizure.

It is suggested that diphenylhydantoin is clinically effective either by raising abnormally lowered seizure thresholds or by reducing energy available for seizure discharges, or both. [Aided by a grant from the Research Fund, Univ of Utah School of Medicine].

The effect of cobalt on the antitubercular activity of aspergillic acid. ANDRES GOTH (introduced by Donald Slaughter), *Dept of Physiology and Pharmacology, Southwestern Medical College, Dallas, Texas*. It has been reported previously (A. Goth, *J Lab & Clin Med* 30: 899, 1945) that ferric ions interfered with the antibiotic activity of aspergillic acid. On investigating the effect of other metals, it was found that the addition of cobaltous ions to various media greatly enhanced the inhibitory properties of aspergillic acid against two human strains of *M. tuberculosis*.

Cobaltous ions in a concentration of 1:50,000 or greater inhibit the growth of *M. tuberculosis*. In a concentration of 1:100,000 the inhibitory activity of cobalt is very slight, but it increases the antitubercular activity of aspergillic acid more than fourfold.

The potentiation of the antitubercular activity of aspergillic acid by cobalt was especially marked in media of low iron content.

Aspergillic acid forms a red complex with cobaltous chloride. When such a complex was injected intramuscularly in a series of ten tuberculous guinea pigs daily in the amount of 50 mg per kg of aspergillic acid and 1 mg per kg of $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$, it proved toxic as evidenced by local inflammatory changes at the site of injection and loss of weight as compared with ten untreated guinea pigs.

The oxidation of tyramine in vitro. WM. M.

¹ Winthrop Research Fellow in Pharmacology

GOVIER, MARY E GRELLIS, NAOMI YANZ and KARL H BEYER *Dept of Pharmacology, Medical Research Division, Sharp and Dohme, Inc, Glenolden, Pa* Tyramine can be oxidized in rat liver homogenates with an oxygen uptake corresponding to three atoms of oxygen per mole of substrate. Although the mechanism of this oxidation is not completely understood at present, it seems certain that the reaction is not entirely catalyzed by monamine oxidase, since monamine oxidase alone usually catalyzes the uptake of only one oxygen atom per mole. Further support to this view is given by the fact that the following components seem necessary for the uptake of three oxygen atoms: monamine oxidase, a dehydrogenase, an intact cytochrome cytochrome oxidase system, and either an α -keto acid or an amino acid capable of being oxidized to an α -keto acid. The finding that phenethylamine, which is usually deaminated by monamine oxidase with an oxygen uptake of one atom per mole, is not oxidized to this extent by our system, is indicative of the dissimilarity of the reaction mechanisms.

Loss of potency of commercial insulin stored at room temperature R LORIMER GRANT (introduced by John H Draize) *Division of Pharmacology, Food and Drug Administration, Federal Security Agency, Washington, D C* Samples of insulin injection, which at the time of their certification by the Food and Drug Administration contained 40 units per cc, were assayed by a modification of the method of Bliss and Marks (Quart J Pharm & Pharmacol 12 182, 1939) after storage at room temperature in Washington, D C from 15 days to 2 years. Losses in potency for periods of storage up to 60 days were not significant. The potency remaining was 85 to 90 per cent after 4 months, 80 per cent after 1 year, and 70-75 per cent after 2 years.

The response of the isolated frog heart to different barbiturates CHARLES M GRUBER and GOLDIE FREEDMAN KEYSER (by invitation) *Dept of Pharmacology, Jefferson Medical College, Philadelphia* These experiments were undertaken to make an extensive comparative study of the effects of the barbiturates on the excised hearts of frogs (*Rana pipiens*). Each animal was pithed and the heart exposed, and the tip of a modified Straub cannula was inserted into the ventricle. The pressure within the ventricle was kept constantly at 2 cm water pressure.

Ringer's solution was employed in perfusing the heart and keeping the outer surface of the organ moist. The sodium salts of the following barbiturates dissolved in Ringer's solution were used: ortal, seconal, amytal, pentobarbital, neonal, butisol, phenobarbital, evipal, vinbarbital, and barbital. The effects of solutions of these drugs in 1/3000, 1/2000, 1/1000, 1/500, and 1/250 molar

concentrations were observed in 388 experiments on 64 isolated frog hearts. According to our findings, all of the barbiturates act qualitatively similarly but quantitatively differently upon the heart. We also noticed that the heart rate usually, though not always, slowed simultaneously with the decrease in the height of the contractions. From the results of these experiments it seems possible to divide the barbiturates studied into three groups: (1) those with marked cardiac depression, ortal and seconal; (2) those with moderate depression, amytal, pentobarbital, and neonal; and (3) those with mild toxic effects, butisol, phenobarbital, evipal, vinbarbital, and barbital.

The effect on rats of daily-life span exposure to cigaret smoke H B HAAG, J H WEATHERBY, DORIS FORDHAM and P S LARSON *Dept of Pharmacology, Medical College of Virginia, Richmond* Beginning at weaning age, a group of 16 white rats (12 females plus 4 males) was exposed, in a suitable chamber, to cigaret smoke every half-hour, fourteen times daily for their entire life span.

The smoke was generated by means of a multiple cigaret smoking machine constructed to simulate as closely as possible human smoking, approximately one 35 cc puff per cigaret being drawn each minute and the chamber being evacuated of smoke between puffs.

One additional group of rats was kept as controls in the animal room ("cage controls") while another ("smoke controls") was treated (except for the smoking) more or less similarly to the experimental ("smoked") ones.

It was found that

1 The average life span of the smoked group was 642 days, of the smoke controls 544, and of the cage controls 631 days.

2 Weekly weight determinations showed that the cage controls attained and maintained the greatest average weight, the smoked group somewhat less, with the values for the smoked controls being intermediate.

3 Blood pressure determinations taken at regular 2 month intervals showed no differences between the three groups.

4 Necropsy observations demonstrated no lesions particularly characteristic of any of the three groups.

The pharmacologic action of some derivatives of benzoylcholine CARROLL A HANDLEY *Dept of Physiology and Pharmacology, Baylor Univ College of Medicine, Houston, Texas* The p-nitro, p-amino, and p-methyl- derivatives of benzoylcholine were prepared and their pharmacologic action studied. These compounds resemble nicotine quite closely in action. In small doses they produce a rise in blood pressure plus respiratory stimulation. The effect on blood pressure may

be completely abolished by blocking the autonomic ganglia with nicotine. Repeated large doses of these agents will also block the ganglia. Choline esterase does not cause hydrolysis, and there seems to be no action peripheral to the ganglia.

The compounds are listed above in order of increasing pressor activity.

Effects of Senecionine on the hamster and monkey. PAUL N. HARRIS, K. G. WAKIM and K. K. CHEN, *Lilly Research Labs and Indiana Univ. Medical Center, Indianapolis*. Senecionine, an alkaloid of *Senecio vulgaris* and *S. integerrimus*, was previously shown to cause death in mice with central necrosis of the liver, and in rats with hypoprothrombinemia. Further investigation was carried out in 15 golden hamsters and 4 rhesus monkeys by intravenous injection. With the former, single doses of 70 to 80 mg per kg resulted in prostration and death on second to fourth day with necrosis of the liver, which was predominantly periportal. Doses of 56 to 62 mg per kg were occasionally fatal with the same lesion in the liver. Repeated injections of senecionine, totaling 30 to 75 mg per kg caused gradual depression, prostration, and death of all 4 monkeys. Three of them developed acute necrosis of the liver which was midzonal or periportal in type. Associated with the hepatic injury, there was increase of plasma prothrombin time and elevation of serum bilirubin. The liver of the fourth animal, for some unknown reason, was normal. Senecionine produced fatty degeneration of the kidneys of all 4 monkeys.

The analgetic potency and acute toxicity of Salicylamide and certain of its derivatives as compared with established analgetic-antipyretic drugs. E. ROSS HART, *Jefferson Medical College, Philadelphia*. With minor modifications the method of D'Amour and Smith has proven suitable for demonstration of analgetic activity of all compounds thus far tried. Using this procedure with the drugs being administered by stomach tube, the relative analgetic potencies of eleven compounds have been found to be as follows: When the potency of Acetylsalicylic acid is arbitrarily assigned a value of 1.0 the potency of Salicylamide becomes 7.5, Diiodosalicylamide 5.3, Sodium salicylate 3.6, Acetanilid 2.6, O-Acetylsalicylamide 2.4, N-Acetylsalicylamide 2.2, Bromosalicylamide 2.2, Antipyrine 2.0, Acetophenetidin 0.8, Aminopyrine <0.6.

The lethal doses (LD₅₀) of these compounds when administered to rats by stomach tube range between 0.6 and 1.3 times that for Acetylsalicylic acid.

Since none of the amides produced convulsions as part of the intoxication syndrome it appears that masking the carboxylic acid group with an amide in salicyl compounds materially alters the action.

On the basis of these findings it would appear advisable to investigate further this class of compounds for useful analgetics.

The effect of diisopropyl fluorophosphate (DFP) on neuromuscular transmission in normal individuals and in patients with myasthenia gravis. A. McGUIRE HARVEY, BENJAMIN F. JONES, SAMUEL TALBOT and DAVID GROB (introduced by Oscar Bodansky), *Depts. of Medicine and Ophthalmology, The Johns Hopkins Medical School, Baltimore, Maryland*. The action of DFP on neuromuscular function has been studied in normal individuals and in patients with myasthenia gravis. Muscle action potentials in response to supramaximal stimulation of the motor nerve were recorded before and at intervals after the injection, and voluntary motor power was tested by means of a hand dynamometer.

When 1.5 mgm of DFP in 3 cc of physiological saline solution was injected into the brachial artery there was diffuse sweating over the forearm and hand. Numerous spontaneous fasciculations appeared which had the visual and electrical characteristics of single motor unit activity. Pronounced motor weakness developed immediately in the injected area. No change took place in the voltage of the muscle potential in response to a single nerve stimulus, but the response became repetitive in nature. When two stimuli were set up the voltage of the response to the second was reduced. These effects of DFP reached their height in 30 to 40 minutes, and were still easily detectable after 96 to 120 hours.

In patients with myasthenia gravis a striking localized increase in muscle strength resulted. No fasciculations appeared, and the characteristic changes in the electromyographic records became normal. The local return of strength remained detectable for 8 to 10 days. When neostigmine was administered subcutaneously just prior to the intraarterial injection of DFP, the latter drug produced no sustained improvement in motor power.

The stimulating action of estrogen on release of luteinizing hormone. ARTHUR A. HELLBAUM and ROY O. GREER, *Dept. of Pharmacology, Oklahoma Univ. School of Medicine, Oklahoma City, and Harvard School of Dental Medicine, Boston, Mass.* The pituitaries of adult female rats, under normal estrogen influence, stimulate moderate luteinization in normal and hypophysectomized recipients. On the other hand, the pituitaries of adult female rats whose estrogen influence has been previously removed by oophorectomy, stimulate extensive luteinization of the recipient ovaries. This indicates that the luteinizing factor is not liberated in the absence of estrogen, but remains stored within the pituitary gland. That estrogen releases the luteinizing factor is suggested also by the type of response produced

by pituitaries from oophorectomized adult female rats which have been injected with estradiol benzoate daily for 30 to 45 days. These pituitaries stimulate follicular development but no corpora lutea, the luteinizing factor having been removed under the influence of the estrogen treatment.

Studies on the pharmacology of cholic acid
 LLOYD W. HAZLETON and REBECCA C. HELLERMAN (by invitation) *The George Washington Univ., The Kalusowski Memorial Research Lab., School of Pharmacy, Washington 6, D. C.* In view of the fact that cholic acid produces catharsis in mice while other bile salts do not, a study to more completely evaluate this compound experimentally was initiated. Data obtained to date indicate that intravenously cholic acid, as the sodium salt, is relatively nontoxic although the transient lowering of blood pressure is greater than that with comparable doses of dehydrocholic acid. After intravenous doses of 50 mg./kg. in dogs the choleresis from sodium cholate is comparable to that from sodium dehydrocholate in volume, but the total solids and bile acid content are markedly greater. Maximum choleresis occurs within the first hour after intravenous administration but can be maintained by repeated administrations over a long period of time. A relatively high percentage of the administered cholic acid can be recovered from the bile during the period of choleresis.

Concurrently with the dog experiments discussed above, experiments using rats are being conducted. It has become apparent that anesthetized rats are convenient for multiple acute experimentation. The flow of bile is higher per kg. of body weight in the rat than in the dog and quantities sufficient for chemical analysis are easily available. Insufficient data are available to make an accurate comparison but it is believed that the rat may be useful in at least preliminary testing. [Acknowledgment is made of a grant from the Proprietary Association in support of this study.]

Evaluation of uterine antispasmodics
 RUSSELL A. HUGGINS (by invitation) and R. A. WOODBURY *Dept. of Pharmacology, Univ. of Georgia School of Medicine, Augusta*. In humans symptoms and tracings typical of dysmenorrhea cannot be produced by acetylcholine, histamine or pitocin, but were produced with pitressin and distention of the uterus. (See these abstracts, Woodbury et al.) Accepted and proposed uterine antispasmodics were tested in animals where uterine activity was induced by pitressin and distention or stretch of the uterus. Many of these animals were pretreated with stilbestrol to increase the irritability of the uterus.

In unanesthetized dogs and rabbits uterine pressures and action potentials were recorded

optically from an intra-uterine balloon and silver chloride coated electrodes. Ephedrine, Trasentin, Pavatrine, morphine, beta-diethylaminoethyl phenyl alpha-thienylglycolate hydrochloride (Stearns #600), beta-diethylaminoethyl phenyl alpha-thienylacetate hydrochloride (Stearns #606), Priscol and magnesium sulfate were evaluated as uterine antispasmodic agents where excessive activity was produced by pitressin or distention.

Many of these drugs were evaluated by the uterine bath method substituting pitressin or uterine stretch as a measure of inducing activity.

Potential of the depressant action of alcohol
 by ADRENALIN H. R. HULPIEU and V. V. COLE *Dept. of Biochemistry and Pharmacology, Indiana Univ. School of Medicine, Indianapolis*. The depression produced by alcohol closely parallels the concentration found in the brain, and blood alcohol always mirrors brain alcohol. The capillaries of the brain must, therefore, be completely permeable to alcohol. These facts form the basis of chemical tests for intoxication. Potentiation of the action of alcohol by previously administered adrenalin has been described by U. Friedemann, who explained it as increased permeability of brain capillaries and named it "auxoneurotropic" action. Our experiments confirm such a potentiation but force us to a different interpretation. If Friedemann's explanation be true, normal brain capillaries are incompletely permeable to alcohol, and it might be argued that any unusual behavior after drinking resulted from release of adrenalin due to excitement. Therefore, we studied the distribution of intravenously injected alcohol alone, and after adrenalin. For a short time, the muscles of rabbits, previously given adrenalin, contained almost no alcohol, while the concentration in their blood and brain remained high. In contrast to this, equilibrium was rapidly established between blood, brain and muscle in the controls. We also found that the dose of adrenalin necessary to produce an "auxoneurotropic" effect was far greater than that released in the body. Furthermore, it has long been known that large doses of adrenalin will cause temporary vasoconstriction in skeletal muscle. Thus when distribution is correlated with the known actions of adrenalin, it is evident that the "auxoneurotropic" action of adrenalin, it is evident that the "auxoneurotropic" action of adrenalin can be explained by alterations in circulation.

Influence of altered acid-base balance and anoxia upon the physiological disposition of certain antimalarial drugs
 JOSEPH W. JAILER (by invitation), CHARLES G. ZUBROD (by invitation), MORRIS ROSENFELD and JAMES A. SHANNON *Research Service, Third Medical Division, Goldwater Memorial Hospital and the Dept. of Medicine,*

New York Univ College of Medicine, New York
An acute alteration in acid base balance with reduction of blood pH to 6.8 resulted in a two to three-fold elevation in plasma level of quinaquine and SN-7618. In typical experiments, one hour exposure to 10 per cent carbon dioxide in oxygen administered intratracheally to dogs raised plasma quinaquine concentration from 559 to 112 gamma per liter, plasma SN-7618 from 113 to 230 gamma per liter.

Severe anoxia with reduction of blood oxygen content to 8 vol per cent exerted no significant effect upon plasma drug concentration. Blood pH was maintained constant because of carbon dioxide absorption in the rebreathing circuit.

Chronic acid-base changes induced in man by oral ingestion of alkaline and acid salts were manifested primarily upon renal excretion of the drugs. Elevation of urinary pH promoted drug retention, reduction in pH favored excretion. Sodium bicarbonate in daily dosage of 20 grams reduced quinaquine excretion to 0.2 per cent of the ingested dose, ammonium chloride, at 8 grams daily, raised excretion to 1 per cent. The plasma drug level remained unaffected since urinary excretion represented at most a minor fraction of drug intake. With SN-6911, where urinary output was changed from 9 per cent to 75 per cent, the plasma level revealed a correlated cycle, rising during the alkaline phase and falling during the acid phase of high excretion. Renal output of SN-7618 reacted similarly to that of SN-6911. [Based upon work done under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and New York Univ.]

Rôle of methemoglobinemia in protection against and treatment of inhalation poisoning by HCN and CNCl. BERNARD J. JANDORF (by invitation) and OSCAR BODANSKY, *Biochemistry Section, Medical Division, Chemical Warfare Service, Edgewood Arsenal, Md.* Chen et al. (Am J Med Sci 188:767, 1934) and others have shown that intravenous injection of nitrites, immediately following subcutaneous injection of NaCN, resulted in an antidotal effect, presumably by competition of the methemoglobin so formed with tissue cytochrome oxidase for the cyanide. It was of interest to determine the extent to which this competitive reaction was effective in *inhalation* poisoning by HCN or CNCl, (a) when symptoms of poisoning were established prior to amyl nitrite administration, and (b) when p-aminopropiophenone methemoglobinemia was induced before inhalation of lethal doses.

Amyl nitrite (0.3 cc), administered by inhalation to dogs 30 to 45 seconds after exposure to 1 to 2 lethal doses of HCN, had no significant effect on their mortality. This treatment reduced significantly the mortality of dogs exposed to 1 to 2 lethal

doses of CNCl from $\frac{1}{2}$ to $\frac{1}{5}$, but was ineffective against higher concentrations. Large groups of mice, exposed to 1 to 2 lethal doses of CNCl followed by amyl nitrite inhalation, also showed significantly higher survival rates than untreated mice.

Methemoglobinemia pre-established by p-aminopropiophenone protected dogs against subsequent exposures to HCN and CNCl. The degree of protection was roughly proportional to the degree of methemoglobinemia, thus, 50 per cent methemoglobin protected dogs against 40 lethal doses of HCN. The pre-established methemoglobinemia protected against the systemic effects of CNCl poisoning, but the degree of protection was not as marked as against HCN because of the subsequent development of pulmonary edema.

Rôle of the placebo in tests for drug discrimination. E. M. JILLINER (by invitation) *Yale Univ, New Haven, Conn.* Each of 4 Analgesics and placebo were tested at least 4 times on each of 700 individuals with chronic headaches. Analysis of the data showed that the usefulness of placebo in such tests goes far beyond the usual procedure of establishing the percentage by which a given analgesic may exceed the effect of placebo. A consistently recurring complex of factors shows that reactors to placebo lack the basic conditions for drug discrimination and that the relative potency of analgesics can be established only on individuals who on several exposures to placebo do not react to it.

A comparative study of substituted phenolic urethanes. NORMAN W. KARR (introduced by Benedict E. Abreu) *Division of Pharmacology and Experimental Therapeutics, Univ of California Medical School, San Francisco.* Three phenolic urethanes previously compared with neostigmine and physostigmine (Fed Proc, 1:154, 1942) have been studied further with respect to their activity on a paralyzed skeletal muscle. These compounds are (1) m-isopropyl-p-dimethyl-amino-phenol dimethyl-urethane methiodide, (2) p-dimethylamino-carvacrol-dimethyl-urethane methiodide, and (3) p-dimethylamino-thymol-dimethyl-urethane methiodide. They differ from neostigmine¹ in that the substituted urethane group and the substituted amino nitrogen are in para position rather than meta and aliphatic side chains are added in ortho and meta positions.

Action on skeletal musculature was tested on the *tibialis anterior* of intact anesthetized cats and dogs, stimulated 30 times per minute through the motor nerve. The paralyzing agents used were β -erythroidine and dihydro- β -erythroidine. Each of the five agents was capable of restoring activity to paralyzed muscles, but they differed in the amount required and the speed with which recovery was

¹ Supplied by Hoffmann-La Roche, Inc., Nutley, N. J.

brought about The order of effectiveness was compound (1) greatest, compound (2) and neostigmine about equal, and compound (3) and physostigmine much less

Acute toxicity in mice was determined by subcutaneous injection and the compounds fell in this order of decreasing toxicity compound (1) 0.0015 mg/kg, compound (2) 0.004 mg/kg, neostigmine 0.01 mg/kg, compound (3) 0.015 mg/kg, and physostigmine 0.03 mg/kg Acute oral toxicities in mice fell into a different order, suggesting differences in the degree or rate of absorption The most toxic orally was neostigmine 13.5 mg/kg, followed by compound (1), 39.8 mg/kg, physostigmine, 47 mg/kg, compound (3), 77.5 mg/kg, and compound (2), 95 mg/kg

Acute subcutaneous toxicity in dogs was estimated by injecting one animal with each compound in doses which increased 50 per cent daily Lethal doses, in order of decreasing toxicity were compound (1) 0.153 mg/kg, compound (2) 0.345 mg/kg, neostigmine 0.769 mg/kg, physostigmine 1.138 mg/kg, and compound (3) 4.60 mg/kg All five dogs showed salivation, defecation, respiratory embarrassment, and muscular twitching before death, and hemorrhage of the bowel mucosa at autopsy There were no other significant gross nor microscopic changes [Aided, in part, by a grant from Merck and Company, Inc., Rahway, N. J.]

Curative effect of plasmoquin in plasmodium lophurae infections F. E. KELSEY, FRANCES K. OLDFHAM and A. L. GITTELSON Dept. of Pharmacology, Univ. of Chicago Result of experiments to obtain a parasitic cure in *Plasmodium lophurae* in chickens with various antimalarial drugs are presented The strain was maintained for over a year by bi weekly transfer into 5 day old birds, and used concurrently for assay of suppressive activity For curative tests, birds were fed the drug incorporated into diet for 2 weeks, commencing two weeks after inoculation with infected blood Two weeks after discontinuation of the drug 2 cc of blood was withdrawn from each bird and one cc injected into each of two 5 day old chicks Preliminary experiments with dilutions of infected blood indicated that with 30 parasites, the infection appeared approximately 2 weeks after inoculation and reached a peak of about 2-5% infected red cells, consequently smears were made on the subinoculated birds on alternate days between the 7th and 28th day after subinoculation If no parasites were observed in the smears, subinoculations were made from the donor birds at approximately 4 week intervals for up to six months unless positive evidence of infection was obtained earlier

Quinine and atabrine were ineffective in curing the birds With plasmochin, the majority of the

birds apparently exhibited complete parasitic cure Spontaneous cure did not occur for at least 7 months as evidenced by subinoculation from infected birds which received no drug [Work done under contract with the Office of Scientific Research and Development]

A mechanism of drug "potentiation" Pamaquin metabolism as influenced by quinacrine THOMAS J. KENNEDY, JR. (by invitation), CHARLES G. ZUBROD (by invitation), FREDERICK S. BIGELOW (by invitation), ROBERT W. BERLINER (by invitation) and JAMES A. SHANNON *Research Service, Third Medical Division, Goldwater Memorial Hospital, and the Dept. of Medicine, New York Univ. College of Medicine, New York* Few quantitative data are available which outline mechanisms responsible for the "potentiating" action of drugs Incidental to studies on the physiological disposition of pamaquin, such a mechanism was uncovered Several aspects of the toxicity of pamaquin, presumably the result of higher plasma pamaquin concentrations, are increased by concurrent or prior administration of quinacrine This increase in concentration is due to a specific action of quinacrine whereby it excludes pamaquin from the physiological mechanisms normally responsible for its metabolism

Oral or intramuscular pamaquin (20 mg base) in the normal human yields maximal plasma drug levels in 1 to 2 hours which fall to negligible concentration in 8 hours When pamaquin is administered to patients who have recently received quinacrine, the maximal plasma pamaquin level is from 2 to 10 times higher and the rate of disappearance far lower When plasma pamaquin curves are determined serially in individuals on 30 mg oral doses of quinacrine daily, maximal plasma pamaquin levels rise progressively and the rate of disappearance of pamaquin approaches zero A minimal upward displacement of the plasma pamaquin curve occurs with a single 10 mg dose of quinacrine, with a single 500 mg dose of quinacrine, this is demonstrable for as long as 6 weeks

The effect of quinine, SN-7618 and other basic organic compounds on the plasma pamaquin curve is not striking [Based upon work done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and New York Univ.]

Cinchona alkaloids 7 The nature of the quinine oxidizing enzyme of liver W. EUGENE KNOX, CART M. C. A. U. S., (introduced by James A. Shannon) *Research Service, Third Medical Division, Goldwater Memorial Hospital, and the Dept. of Medicine, New York Univ. College of Medicine, New York* The enzyme of rabbit liver which oxidizes quinine to its carbostyryl has been prepared in about 5% purity It is a flavoprotein

containing 0.7 gammas of riboflavin per unit of activity. This flavin is reduced anaerobically by cinchonidine. The enzyme reacts directly with oxygen with the formation of hydrogen peroxide but reacts more rapidly with methylene blue. It is rapidly destroyed during the catalytic process, has an optimum pH at 7.4 to 7.6, a maximal rate with cinchonidine concentrations above 2.0×10^{-4} M and is not inhibited by higher concentrations. Routine assay involves the use of the rate of methylene blue reduction with cinchonidine as substrate.

The enzyme can oxidize other compounds all of which have an active α -hydrogen in a heterocyclic ring. The reaction is limited to the replacement of the active hydrogen by a hydroxyl group. In addition to the cinchona alkaloids the enzyme catalyzes the oxidation of quinoline, quinoline derivatives, isoquinoline, indole, pyrrole and some pyridine derivatives. The physiological compound most rapidly oxidized is N¹-methyl nicotinamide.

The enzyme has properties similar to and is not dissociable from the flavoprotein liver aldehyde oxidase. All flavoprotein present can be accounted for by the aldehyde oxidase as well as by the quinoline oxidizing enzyme. The simultaneous oxidation of the two is slower than their separate rates. Quinine carbostyryl is reducible to quinine by the simultaneous anaerobic oxidation of aldehyde. The enzyme, therefore, seems to be a duo functioning flavoprotein analogous to xanthine oxidase. [Based upon work done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and New York Univ.]

The chronic toxicity of di-isopropyl fluorophosphate in dogs, monkeys and rats. GEORGE B. KOELLE (by invitation) and ALFRED GILMAN, *Pharmacology Section, Medical Division, Chemical Warfare Service, Edgewood Arsenal, Md.* The chronic toxicity of di-isopropyl fluorophosphate (DFP) has been studied in dogs, monkeys and rats prior to its clinical trial in myasthenia gravis and glaucoma. Four dogs received doses ranging from 0.05 to 0.30 mg DFP/kg, intramuscularly, twice weekly for 24 weeks. No significant changes occurred in blood sugar, serum protein, plasma NPN, hepatic function, red and white cell counts or differential counts. All showed sporadic nicotinic symptoms and marked depression of serum and red cell cholinesterase. One dog developed slight cardiospasm. Four monkeys receiving 0.03 to 0.05 mg DFP/kg, intramuscularly, twice weekly for 16 weeks gave similar results, although three developed bronchopneumonia and no cardiospasm appeared. Three groups of 12 rats each on dose levels of 0.1, 0.3 and 0.5 mg DFP/kg, intramuscularly, twice weekly for six months, showed no significant differences in growth rates and only

occasional slight signs of nicotinic fibrillation, diarrhea and chromodachryrhea. Determinations of brain cholinesterase activity done terminally on four rats from each group gave average figures of 65, 28 and 21 per cent of normal respectively. No significant autopsy findings were obtained in any of the above animals.

Two dogs were maintained on high doses (0.3 and 0.5 mg/kg, intramuscularly, three times weekly) for 12 weeks. Both developed severe nicotinic fibrillation, transient muscarinic signs (bronchoconstriction, hypersalivation, diarrhea), and persistent urinary incontinence, hindleg paralysis and cardiospasm resulting in extreme esophageal dilatation. The last persisted after injections were stopped and was the eventual cause of starvation and death in both dogs.

Dimethylpiperidines as primary ganglionic depressants. THEODORE KOPFANYI and A. EARL VIVINO (by invitation), *Georgetown Univ., School of Medicine.* While studying the nicotinic action of drugs, the hydrochlorides of piperidine, propylpiperidine (conune), 2,3 and 2,4 dimethylpiperidines were employed intravenously in dogs, cats and rabbits anesthetized with sodium pentobarbital. The cardiac responses following peripheral vagus stimulation, blood pressure changes and responses of pupil and nictitating membranes were used as criteria of ganglionic stimulation or depression.

Piperidine and propylpiperidine, given intravenously in doses of from 5-10 mg per kg body weight have, even upon oft repeated injection, an initial stimulant and secondary depressant effect on both parasympathetic and sympathetic ganglia, while 2,3 and 2,4 dimethylpiperidines, in the same doses and by the same route, produced varying degrees of ganglionic depression without initial stimulation. (Usually total doses of 25-40 mg per kg were sufficient to produce complete ganglionic paralysis determined by the criteria used.) While piperidine produced a profound and propylpiperidine a slight pressor effect, the dimethylpiperidines produced depressor and no pressor effects. Piperidine is a respiratory stimulant of the nicotine type, while dimethylpiperidines produced no respiratory changes. 2,3 and 2,4 dimethylpiperidines gradually abolished (a) the electrical excitability of the cardiac vagus, (b) the pressor effect of intravenously injected nicotine, and (c) the mydriatic and related sympathetic ocular effects following the stimulation of the cervical sympathetic. If the stimulation of the latter nerve was carried out on the postganglionic instead of the preganglionic division, the pupillary and other ocular responses were still obtainable. Dimethylpiperidines have no effect on the muscarinic action of intravenously injected acetylcholine.

Piperidine and propylpiperidine produced a contraction of the rectus abdominis of the frog

while dimethylpiperidines produced no stimulation of this skeletal muscle. On the contrary, they prevented the stimulating effects of acetylcholine but not of potassium.

These experiments suggest that while drugs of the nicotine or conine type are primary ganglionic stimulants and depress the ganglia only after large doses and following primary stimulation, 2,3 and 2,4 dimethylpiperidines are devoid of this primary stimulating effect and act as atropine does on the parasympathetic terminations or cocaine on the sensory nerve ends.

Synergisms and antagonisms between physostigmine and di-iso-propyl fluorophosphate. RUDOLF KOSTER (introduced by McKeen Cattell) *Dept of Pharmacology, Cornell Univ Medical College*. Physostigmine exerted a marked protective action against the toxic effects of subsequent doses of di-iso propyl fluorophosphate. The best results were obtained when fluorophosphate was given at a short interval after the largest dose of physostigmine compatible with survival. Symptoms were less severe and it was possible to save all animals from three times the LD50 dose of the fluorophosphate and many from six times the LD50 dose. With larger doses of physostigmine made possible by the previous injection of atropine animals survived more than 30 times the LD50 dose. The opposite was true when the drugs were given in reverse order, i.e., animals which had received sublethal doses of the fluorophosphate were extremely sensitive to subsequent doses of physostigmine, an effect which lasted over a period of months and was still present at a time when the serum cholinesterase had recovered its normal activity.

Cats receiving iso propyl-fluorophosphate had enhanced sensitivity to subsequent injections of the same compound, which persisted for many days. On the other hand cats receiving physostigmine alone did not become more sensitive or more resistant with repeated doses at intervals of 4 to 24 hours.

Physostigmine did not prevent the fall in cholinesterase activity of the serum in cats subsequently poisoned with iso propyl-fluorophosphate. However, the experiments done in the Research Laboratories of the Chemical Warfare Center at Edgewood Arsenal (Personal communication) demonstrating that physostigmine completely protects cholinesterase from inactivation by the fluorophosphate in vitro, makes it probable that this mechanism is concerned in the cat experiments. [The work described in this abstract was done under contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Cornell Univ Medical College.]

The anesthetic properties of n-propyl methyl ether JOHN C. KRANTZ, JR. *Dept of Pharmacology,*

School of Medicine, Univ of Maryland, Baltimore. n-Propyl methyl ether produces a desirable anesthetic syndrome in several species of animals. Its potency is approximately 20 per cent greater than that of its isomer, ethyl ether. Abdominal relaxation produced by the inhalation of this compound appears to be greater than that produced by ethyl ether. With prolonged and repeated anesthetics there was no damage to important viscera in the rat, dog and monkey. In human anesthesia, the compound is less irritating than ethyl ether, produces less disagreeable postanesthetic sequelae and elicits a more relaxed abdominal musculature.

The effect of nephrectomy on the "elimination" of Ouabain by the cat STEPHEN KROP *Dept of Pharmacology, Yale Univ School of Medicine, New Haven, Conn.* (Read by title.) Though the liver is considered to be the site of inactivation of the cardiac glycosides, the possibility that the kidneys participate to a significant extent in their "elimination" has received little attention. It appeared desirable to obtain information relating to this possibility, especially because the data supporting the liver inactivation hypothesis were obtained with very high doses in animal species whose tolerance is very great. Normal and bilaterally nephrectomized cats were used in the present study. Ouabain was selected because of its comparatively brief duration of action, so that substantial "elimination" could be expected well within the time that the animals remained in good condition following bilateral nephrectomy. Six cats were nephrectomized under ether anesthesia and 1 to 2 hours later were given 0.05 mg ouabain (USP Reference Standard) per kg intravenously. Simultaneously six control cats were similarly treated except for nephrectomy. Twenty-four hours later, both groups of animals were "titrated" with dilute ouabain solution in physiological saline until death. The mean lethal doses of ouabain for these two groups of animals did not differ significantly from each other and not greatly from that of six normal control animals studied simultaneously. Variations in acute sensitivity were ruled out by a simultaneous sensitivity test in six normal cats. It is concluded that normal cats do not "eliminate" ouabain as rapidly as commonly believed, and that the kidney in the cat does not participate demonstrably in the "elimination," at least in the first 24 hours. Whether this situation obtains after longer periods and for different cardiac glycosides remains for future study. [Aided by a grant from the Fluid Research Fund of Yale Univ School of Medicine.]

The effect of succinate on pentobarbital toxicity and narcosis in the cat STEPHEN KROP *Dept of Pharmacology, Yale Univ School of Medicine, New Haven, Conn.* (Read by title.) It has been contended that succinate reduces the toxicity of and shortens the narcosis induced by pentobarbital.

procedures Insulin-dextrose actually retarded the metabolism of the alcohol to a significant degree The amount of alcohol appearing in the urine was not significantly influenced Blood and urine acetone concentrations showed little or no changes from the control values The preponderance of evidence indicates a lack of any action on the metabolism of isopropyl alcohol by the various combinations tried

The effects of di-isopropyl fluorophosphate upon normal and glaucomatous eyes IRVING H LIO-ROLD (by invitation) and JULIUS H COMROF, JR Depts of Ophthalmology and Pharmacology, Univ of Pennsylvania School of Medicine, Philadelphia Di-isopropyl fluorophosphate (DFP) instilled locally in human eyes produced prolonged miosis (6-27 days), ciliary spasm and false myopia (2 days) and decreased intraocular tension (1-8 days) without any local irritation DFP failed to contract the totally denervated cat iris, its effects therefore are due entirely to the inactivation of cholinesterase caused by DFP One or two instillations of 0.1 or 0.2% DFP overcame and outlasted the cycloplegic effect of 4% homatropine or 1% atropine Little if any systemic absorption of DFP (measured by change in plasma ChE levels) occurred following its ocular use

DFP has been used in the treatment of 76 glaucomatous eyes (52 patients) previously treated with physostigmine and/or pilocarpine In 16 instances no miotic lowered the intraocular tension satisfactorily In 24 cases, each miotic was able to maintain the tension below 30 mm Hg In the other 36 cases, physostigmine and/or pilocarpine failed to reduce intraocular tension to normal, in these, DFP maintained normal tension and prevented further loss of visual fields The duration of action of DFP greatly exceeded that of pilocarpine and physostigmine Instillation of the latter drugs was required 3 to 6 times daily while DFP was required more than once daily in only 10 cases, once daily in 17 patients, once every two days in 2, every 3 days in 12, every 4 days in 10, 5 days in 6, 7 days in 2, and 10 days in 1 Undesired effects were visual blurring, brow and eye ache, spasm of accommodation and pericorneal vasodilation [*Done under contract with Medical Division, Chemical Warfare Service*]

Determination of minute quantities of sulfanilamide derivatives in biological samples J T LITCHFIELD, JR, L ALONSO, and L GODDARD *Chemotherapy Division, Stamford Research Labys American Cyanamid Company* The practical limit of sensitivity of the Bratton-Marshall procedure for determination of sulfanilamide derivatives is reached when the concentration of the drug present approaches the magnitude of the blood or plasma blank A simple procedure was devised by which the sulfanilamide derivative is extracted from

plasma with chloroform The drug is then extracted from the chloroform with a small quantity of acid to which is then added the reagents used in the Bratton Marshall procedure The final volume need be no greater than one cubic centimeter and can represent, if desired, the drug derived from 95% of the original sample of plasma Readings are made in a Coleman clinical spectrophotometer using a microcuvette designed for a volume of 0.5 cc With this procedure the plasma blank is almost negligible Thus, by elimination of the dilution of the sample ordinarily necessary for protein precipitation, the sensitivity of the Bratton Marshall procedure can be increased at least ten fold This increase in sensitivity makes possible the determination of unusually low drug concentrations

The anti-histamine and atropine-like properties of quaternary ammonium derivatives of Benadryl. E R LOEW, MARGARET E KAISER and MONA ANDERSON (introduced by Carl C Pfeiffer) *Dept of Pharmacology, Univ of Illinois, College of Medicine, Chicago, Illinois, and Parke, Davis and Company, Detroit, Mich* B-Dimethylaminoethyl benzhydryl ether hydrochloride (Benadryl), a tertiary amine, in an anti-histamine compound since its most characteristic action is to decrease or annul such pharmacological actions of histamine as bronchoconstriction in guinea pigs, depressor effect in dogs and the spasmogenic action on isolated guinea pig ileum Although Benadryl is predominantly a histamine antagonist, it also possesses atropine-like properties since it decreases the depressor and spasmogenic actions of acetylcholine (ACh)

The quaternary derivatives of Benadryl found to possess the most pronounced anti-histamine and atropine-like properties were the methiodide, methylchloride, methyl p-toluenesulfonate and methyl methylsulfate In view of the well known muscarinic, nicotinic and curare-like actions of numerous quaternary ammonium compounds, including choline and its esters, it is considered significant that these derivatives of Benadryl, which are choline derivatives, induce pronounced atropine-like actions The replacement of muscarinic by atropine-like action in these choline derivatives was demonstrated by inducing mydriasis in rabbits, antagonizing the depressor action of ACh in dogs and inhibiting the spasmogenic action of ACh on isolated guinea pig ileum In addition to the atropine-like action, each quaternary compound possesses marked anti-histamine action, for on a dosage basis all were more effective than Benadryl in preventing fatal histamine-induced bronchoconstriction in guinea pigs

The antagonism between ACh and these choline derivatives suggests that competition of analogs for some cellular component may be involved Consideration must be given to the fact that the same

compounds, chemically unrelated to histamine, are potent histamine antagonists

A preliminary survey of certain lactone antibiotics E L McCawley, B A RUBIN and (by invitation) N J GIACOMINO *Depts of Pharmacology and of Bacteriology, Yale Univ School of Medicine* Two simple lactones found in plants, parasorbic acid and anemonin, have previously been shown to depress the growth of certain bacteria, molds, and yeasts A series of analogous derivatives were subjected to a preliminary pharmacological survey The compounds tested include 3 pentene-1,4-olide (α angelica lactone), 2 pentene-1,4-olide (β angelica lactone), 2,4 pentadiene-1,4-olide (proto anemonin), anemonin (the dimer of proto anemonin), 2 pentene, 5 carboxy-1,4-olide (crotonolactone γ acetic acid), 2 hexene-1,5-olide (parasorbic acid) and 1,5 hexanolide

Proto anemonin was eliminated early from the survey, although it possesses high antibacterial properties *in vitro*, it is a potent vesicant, sternutator, and lacrymator

Anemonin solutions inhibit growth *in vitro* of *Staphylococcus aureus* and *Shigella dysenteriae* at dilutions of 1 12,500, the other derivatives were inactive at 1 2200 The growth of *Escherichia coli* was not affected Anemonin, 3 pentene-1,4-olide, crotonolactone γ acetic acid, and parasorbic acid at dilutions of 1 50,000 prevented the growth of *Trypanosoma equiperdum* *in vitro* Anemonin, 100 mg/kg, injected into the abdominal cavity, failed to protect mice from a *Shigella* peritonitis

Solutions of all of these substances, except 1,5 hexanolide, are irritating when instilled into rabbits' eyes The irritation results in a veno spasm following intravenous injection After intravenous administration in cats there is a transitory fall in blood pressure None of the derivatives cause a change in tone of the isolated rabbit duodenum although the rhythmic contractions may be slowed There is no antagonism to spasms of smooth muscle evoked by acetyl choline, barium or histamine

The LD₅₀'s for oral administration in mice range from 400 to 2500 mg/kg, in relative order 2 pentene 1,4-olide, 2 hexene-1,5-olide, 3 pentene-1,4-olide and 1,5 hexanolide Deaths occur at 400 mg/kg after intraperitoneal injection With anemonin 8 successive 50 mg/kg intraperitoneal doses were tolerated without loss in weight [Aided by a grant from the Fluid Research Fund of Yale Univ School of Medicine]

Certain aspects of the toxicity of diallyl phthalate W A McOWIE¹ (introduced by Hamilton H Anderson) *Division of Pharmacology and Experimental Therapeutics, Univ of California Medical School, San Francisco* The diallyl ester of a ph-

thalic acid (C₁₂H₁₄O₄) is used in industry as a monomer in the manufacture of thermosetting plastics Its toxicity was investigated primarily from the standpoint of the hazard which might follow skin and mucous membrane exposure, since it is a high boiling compound (175°C -9 mm Hg) No gross effect such as erythema or desquamation was noted on the skin of the rabbit from 15 exposures, averaging 5 hours each, to approximately 100 sq cm of shaven abdomen The compound was instilled into the rabbit's eye and the extent of irritation graded by the scoring method of Draize et al (J Pharmacol and Exper Therap 82 377, 1944) No significant difference was found between the one hour scores of diallyl phthalate (score = 1) dibutyl phthalate (score = 2) and ethylene glycol (score = 2) All were relatively non-irritating and caused only a mild and transient conjunctivitis The ester was rubbed gently by means of a glass rod into the shaved back of the rabbit and guinea pig One rabbit died after application of 2.8 ml/kg to approximately 14 per cent of the body surface, 2 rabbits died after 3 and 5 applications respectively of 3.8 ml/kg on approximately 14 per cent of body surface Two rabbits survived without apparent effect 12 exposures, each of 1.6 ml/kg, on approximately 5 per cent of body surface Autopsy of animals which died revealed mild skin inflammation in the area exposed, hepatitis and lung congestion * One guinea pig died after 7 exposures of 5.5 ml/kg, 3 others survived 12 exposures ranging from 2.1 to 4.0 ml/kg One rabbit died 3 hours after 1.5 ml/kg was given intragastrically Death was preceded by diarrhea and prostration Two rabbits survived 1.0 ml/kg intragastrically One rabbit was killed by 1.0 ml/kg given subcutaneously, 2 others survived 0.5 ml/kg by the same route

It would appear from these results that diallyl phthalate is one of the most toxic of the o phthalic acid esters that have been studied This is in agreement with the statement of Shaffer et al (J Ind Hyg and Toxicol 27 131, 1945) that the toxicity of such compounds largely resides in the alkyl portion of the molecule

Toxicity ratios of some cardiac glycosides as influenced by the experimental time G MARESH and A FARAH (introduced by O KRAJER) *Dept of Pharmacology, Harvard Medical School, Boston, Mass* The most frequent method used for determining the comparative toxicity of cardiac glycosides has been some modification of the Hatcher-Magnus method Mehnert (Arch f exper Path u Pharmacol 184 181, 1936), Straub (Straub, W, E Triendl, and J Bode, Arch f exper Path u Pharmacol 199 427, 1942) Hildebrandt (Hildebrandt, H and M P Geppert, Arch f exper Path

¹ Aided by a grant from the Shell Development Company Emeryville California.

* Dr Warren L. Bostick Division of Pathology examined sections of tissues

u *Pharmakol* 199 568, 1943), and Farah (J *Pharmacol and Exper Therap* in press) have shown that the lethal dose (L D) of a cardiac glycoside is dependent on the experimental time as well as the rate of administration of this glycoside. Furthermore it is possible by continuous infusion methods to determine the minimal lethal dose (M L D) of a cardiac glycoside (Melnert, H, *Arch f exper Path u Pharmakol* 184 181, 1936, Farah, A J *Pharmacol and Exper Therap*, in press)

In Table 1 the influence of experimental time upon the L D of g-strophanthin, digoxin, and digitoxin has been compared. It is apparent that an increase in the experimental time reduces the lethal dose as well as the toxicity ratio of these glycosides. From this it must be concluded that any data obtained by limiting either the rate of administration or the experimental time does not give a true picture of the comparative toxicity. It is probably more accurate to determine the M L D by continuous infusion methods and use these values for comparison. It should be emphasized that the rate of administration and experimental time with which the minimal lethal dose is obtained is a characteristic value for each cardiac glycoside.

Experi- mental time in minutes	L D* g stroph, micro- mols per kg	L D digoxin, micro- mols per kg	L D digoxin L D	L D* digitoxin, micro- mols per kg	L D digitoxin L D
30	260	650	2 50	1 27	4 88
60	200	420	2 10	775	3 87
90	170	315	1 85	550	3 23
120	160	275	1 70	430	2 69
180	125			315	2 52
240	175			290	1 60

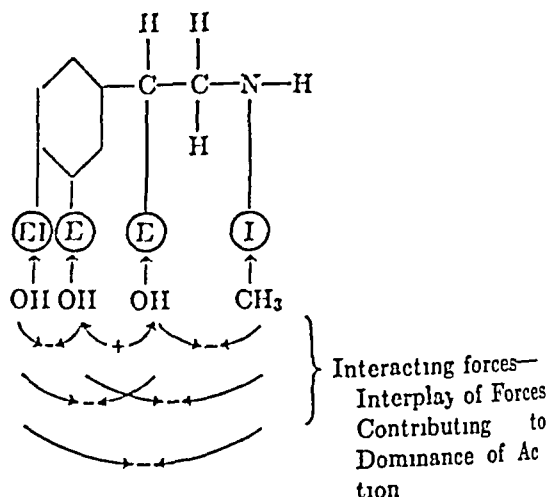
Inhibitory potency of sympathomimetic amines and their ganglionic inhibitory action. AMEDEO S. MARRAZZI and ROSE N. MARRAZZI, *Dept of Pharmacology and Therapeutics, Wayne Univ College of Medicine, Detroit, Mich.* The inhibitory effect of a series of sympathomimetic amines was tested on the superior cervical sympathetic ganglion (cat) where epinephrine had been shown to have a specific inhibitory action in minute doses. All 21 amines tested were found to inhibit synaptic transmission, as indicated by reduction of the post-ganglionic action potentials, to varying degrees not paralleling pressor effects.

Since the activity to be inhibited is initiated by electrical stimuli in a constant and controlled fashion, the technique has advantages over other methods. Comparison with similar series tested on other tissues shows that the order of inhibitory activity in the superior cervical ganglion follows that at other adrenergic sites and that the gang-

lionic synapses, as much as any one tissue can, constitute a valid test object for adrenergic inhibition.

Relating drug structure to sympathomimetic action proved most successful when correlation was made not merely to one type of sympathomimetic action but to both the inhibitory and excitatory (pressor) actions together since the chemical structure is responsible for both simultaneously. The ratios of inhibitory to pressor activity show the degree of predominance of one or the other.

The bare sympathomimetic nucleus was found to inhibit. The influence of added groups are indicated in the accompanying diagram.



Intrinsic action—1°

(E) = Excitation favored

(EI) = Variable effect

Change in dominance small

(I) = Inhibition favored

Interaction—2°

+ = Enhancement

- = Counteraction

The empirical findings are found consistent with a theoretical explanation of molecular activity in relation to cell surface. Compounds with marked predominance, if not exclusive singleness, of action are therapeutically advantageous. (Aided by grants from the Therapeutic Research Committee of the Council on Pharmacy and Chemistry of the American Medical Association and from the Smith, Kline & French Labs.)

Acute and chronic toxicity studies of pyribenzamine hydrochloride (N'-pyridyl-N'-benzyl N dimethylethylenediamine HCl). DONALD MATHIESON (by invitation), HARRY W. HAYS (by invitation), DOROTHY CHESSE (by invitation), ANNE CAMERON (by invitation) and FREDERICK F. YONKMAN, *Dept of Pharmacology, Research Division, Ciba Pharmaceutical Products, Inc., Summit, New Jersey.* Previously, it has been reported

* Data of Hildebrandt (Hildebrandt, H. and M. P. Geppert, *Arch f exper Path u Pharmakol* 199 568, 1942)

(Feder Proc 4 133, 1945) that the MLD50 of pyribenzamine HCl (*N'*-pyridyl-*N'*-benzyl-*N*-dimethylethylenediamine HCl) subcutaneously in white rats was 250 mg per kg for females and 350 mg per kg for males. It has since been learned that castration of female rats renders such animals as resistant to pyribenzamine as normal males. The probability that the administration of estrogens to castrate female rats reduces this resistance, is still a moot point. This indicates that the toxicity of pyribenzamine, like certain other drugs, varies not only with the species but also with the sex.

The gastric instillation by the daily intubation of white rats of both sexes of pyribenzamine HCl in doses ranging from 3 to 5 mg per kg for a period of 5 months has had no deleterious effect on erythrocytes, white cells and their differential distribution, hematocrit value, body weight, appetite, reproductive capacities, gastrointestinal functions and general appearance and comport. In all respects rats fed pyribenzamine were comparable to those controls that were likewise intubated and given by gastric instillation equivalent volumes of tap water.

Offspring of pyribenzamine-fed rats are now being treated and studied like their parents; these have shown no deviations from normal after 5 weeks of treatment. Similar studies are contemplated in 2 more successive generations of these white rats before final conclusions are drawn concerning the chronic toxicity of pyribenzamine in this species.

The protective action of atabrine against chloroform-adrenaline ventricular fibrillation. K. I. MELVILLE, *Dept of Pharmacology, McGill Univ Montreal, Canada*. In dogs under pentobarbital anesthesia with artificial respiration, administration of chloroform vapor for 3 to 5 minutes followed by an intravenous injection of adrenaline (0.02 mg per kg) regularly induced ventricular fibrillation. This effect also occurs after atropinization and double vagotomy.

Under similar conditions, the injection of atabrine hydrochloride in suitable dosages, just prior to or during the chloroform administration, protects the heart against this deleterious effect of adrenaline. This protective action of atabrine lasts only for 10 to 30 minutes, and in all such experiments repetition of chloroform and adrenaline then induced the usual fibrillation.

This action of atabrine is also demonstrable after atropinization and double vagotomy. It appears however to persist for a much longer time after atropinization with the vagi intact than after atropinization and the vagi sectioned.

Electrocardiograms and blood pressure tracings associated with these effects will be presented, and the possible significance of these findings discussed.

Dosage-response to mercurhydrin in patients with heart failure. WALTER MODELL, HARRY GOLD and DONALD A. CLARKE (by invitation) *Dept of Pharmacology, Cornell Univ Medical College, and Cardiac Services of the Beth Israel Hospital and Hospital for Joint Diseases, New York, N. Y.* Dosage response to Mercurhydrin was determined in 69 ambulatory patients suffering from the common types of heart disease. The patients were in a state of advanced cardiac failure, and required mercurial diuretics because digitalis was not sufficiently effective to maintain a reasonable degree of comfort. All patients received a fixed dose of digitalis during the course of the investigation. Patients were weighed before and about 15 hours after the intravenous injection of the mercurial. The loss of weight was taken to represent the extent of the diuresis. In 32 of these patients (88 trials) the average weight change over the 15 hour period, without injection of the diuretic, was 0.56 lbs. The 69 patients received injections of 10 different doses of the diuretic, starting with 0.25 cc and increasing by increments of 0.25 cc, up to doses of 2.5 cc. A dosage-response curve was constructed with the data collected after 773 injections. The curve proved to be typically sigmoid in shape with the steepest part in the range from 0.5 to 1.5 cc, representing average weight-losses of from 2.0 to 4.35 lbs respectively, being flatter at lower dose levels and reaching a ceiling at the 2.25 cc dose. This indicates that the greatest sensitivity to this drug for most patients lies in the range between 0.5 and 1.5 cc, that quantitative comparisons of these diuretics can best be made in this range, and that the greatest clinical effects per unit weight of the drug may be expected from such doses.

Central impairment of sympathetic reflexes by plasmochin. GORDON K. MOE and M. H. SEEVERS, *Dept of Pharmacology, Univ of Michigan*. Plasmochin hydroiodide administered orally to dogs in daily doses equivalent to 5 mg of base per kg leads in three to six days to ocular changes suggesting sympathetic paralysis: enophthalmos, pupillary constriction, and relaxation of the nictitating membranes. At the time that eye signs were readily apparent, six animals were sacrificed in acute experiments designed to locate the site of action of the drug. All results indicate that the functional impairment lies in the central nervous system rather than ganglia or peripheral structures. Complete recovery of function is slow in survivors judging by the gradual disappearance of eye signs over several weeks.

Blood pressure, heart rate, and respiration were recorded; all experiments were done under intravenous Pentothal-barbital sequence anesthesia. Initial mean arterial pressure and heart rate in treated animals averaged 90 mm Hg and 103

beats-min, as compared with 151 and 180 in nine control animals. The following procedures failed to cause significant elevation of pressure or heart rate in the treated animals, but were routinely effective in controls:

- 1 Bilateral carotid occlusion
- 2 Stimulation of the central end of the vagosympathetic trunk
- 3 Occlusion of the trachea

Ganglionic and peripheral transmission were unimpaired, as judged by the ocular responses to preganglionic stimulation of the cervical sympathetic and the cardioaccelerator response to preganglionic stimulation of the stellate ganglia. Cardioaccelerator reflexes were intact, as demonstrated by the bradycardia and dropped beats occurring after injection of epinephrine. [Work done under contract with the Office of Scientific Research and Development]

Toxicity of certain halogenated aliphatic acids for mice JAMES L. MORRISON, *Pharmacology Lab., School of Medicine, Emory Univ., Ga.* The acute oral toxicity of a group of halogen substituted fatty acids ranging from monochloroacetic through α -bromocaproic was determined in mice. The p*H* of a 5 per cent aqueous solution of the compounds studied varied from 0.5 to 2.00. Preliminary tests disclosed a local irritating factor in the effects. To avoid this the 5 per cent solutions of the acids were neutralized (p*H* 7.0) with sodium carbonate, and used at once since solutions of the sodium salts of many of the compounds hydrolyze rather rapidly. Adult white mice, fasted for 24 hours previously, were used throughout as the test animal. To groups of 30 animals varying volumes of each of the neutralized halogenated acid solutions were administered by way of the esophagus with a tuberculin syringe and a large bore blunt hypodermic needle. All animals which died within 5 days were considered, arbitrarily, to have been killed by the compound, since no deaths occurred among a large group of control animals from the same litters. From the accumulated data toxicity curves were plotted and the LD₅₀ for each agent was estimated. Results indicate that the toxicity increases in relation to the increase in molecular weight of the substituted halogen and decreases as the carbon chain is lengthened. Substitution of halogen in the beta position markedly reduces the toxicity as does branching of the carbon chain.

Quantitative studies on intradermal wheals I. Pressure required to produce cutaneous wheals W. GLENN MOSS (by invitation) and C. C. PFEIFFER, *Dept. of Physiology and the Dept. of Pharmacology of the Univ. of Illinois College of Medicine, Chicago, Illinois*. Using optical methods for recording, and a glass spoon calibrated up to 3,000 mm of mercury, it was found that the pressure required to raise an intradermal wheal varied

between the extremes of 1,000 and 3,200 mm of mercury. A sidearm tuberculin syringe fitted with a 27-gauge needle was used to inject the 0.9% sterile NaCl solution. Most subjects required pressures in the range of 1,500 to 2,500 mm of mercury. No sexual or racial differences were noted. Daily variation was as much as 500 mm mercury. The pressure required varied inversely with the depth of the needle in the corium. When the needle was introduced with the bevel up, greater pressures were required, presumably due to the resistance of the inelastic outer layer of the corium. The addition of histamine diphosphate 1/100,000 to the saline did not result in a decrease in the pressure needed to produce the wheals. Typical tracings of the pressure changes were obtained.

Atomic changes produced by streptothricin CHARLES W. MUSHETT and HARRISON S. MARTLAND (introduced by Hans Molitor), *Merck Inst. for Therapeutic Research, Rahway, N. J. and City Hospital, Newark, N. J.* The oral and parenteral administration of streptothricin produced severe pathological changes in laboratory animals. Fatty metamorphosis in the parenchyma of both the kidney and liver appeared early and was often followed by necrosis. A single intravenous injection of 300,000 units per kg or 3 injections of 40,000 units per kg caused in the dog a toxic hepatitis and an extensive tubular nephritis. In such animals there was widespread necrosis of the tubular epithelium, and desquamated cells and hyaline casts were seen in the lumina of the tubules. Some of the tubules also contained metastatic deposits of calcium. Daily doses of 20,000 units per kg intramuscularly for 5 days or 10,000 units per kg orally for two months brought about similar degenerative changes in the monkey. Some of the dogs treated parenterally showed, in varying degree, congestion and/or hemorrhage along most of the intestinal tract. Both dogs and monkeys which were treated parenterally or orally with streptothricin developed ulcerative lesions with marked suppuration and necrosis in the tongue, lips and buccal mucosa. The administration of large doses of riboflavin and nicotinic acid along with the streptothricin failed to prevent the development of these oral lesions. Local necrosis resulted from the intramuscular or subcutaneous injection of streptothricin.

Physiological properties of a new series of sympatholytic agents MARK NICKERSON (by invitation) and LOUIS S. GOODMAN, *Dept. of Pharmacology, Univ. of Utah School of Medicine, Salt Lake City, Utah*. Members of a new series of compounds related to dibenzyl- β -chloroethyl amine have been found to block and reverse excitatory adrenergic responses in mice, rats, rabbits, cats, dogs, and humans. After their administration to dogs and cats, intravenous epinephrine in doses as

high as 4 mg/kg (2000 times the amount normally producing a 40 to 70 mm Hg rise in blood pressure) causes a 20 to 40 mm Hg fall. Actions of other sympathomimetic amines are also both blocked and reversed. The excitatory effects of endogenous epinephrine and adrenergic nerve impulses are similarly blocked, and the normal anoxic rise in blood pressure becomes a fall. Unanesthetized cats given these agents exhibit a marked extension of the nictitating membrane, ptosis, and an absence of mydriasis in dim light. Inhibitory responses to epinephrine, such as relaxation of the non-pregnant cat uterus, are not altered.

Although these compounds lose their activity at body pH, the blocking effect of a single dose may last for 3 to 4 days. This suggests prolonged inhibition or perhaps actual destruction of some structure or substance involved in the excitatory responses to epinephrine and its slow reactivation, repair or replacement. Recovery is without residue.

These amines are only moderately toxic. Young rats given three times the blocking dose daily for two months showed no permanent ill effects, and only a slight growth retardation. Large doses produce coordinated clonic convulsions. The compounds are effective by all routes, but local necrosis may result from subcutaneous and intraperitoneal administration. [This investigation was supported by a grant from Givaudan Delawanna, Inc.]

Relation of structure to activity in a new series of sympatholytic agents. MARK NICKERSON (by invitation), GEORGE NOMAGUCHI (by invitation) and LOUIS S. GOODMAN, *Dept. of Pharmacology, Univ. of Utah School of Medicine, Salt Lake City, Utah* (Read by title). Dibenzyl β -chloroethyl amine and its salts with both organic and inorganic acids are potent sympatholytic agents (see accompanying abstract). At least one benzyl group is essential for this activity and cannot be replaced by an aliphatic chain, a phenyl ring, or a phenylethyl group without complete inactivation. Most substitutions on the benzyl ring (Cl, p-propyl, etc.) also lead to inactivation. A p-methyl substitution does not cause inactivation, but considerably delays the onset of sympatholytic action.

The chloroethyl group, or a similar bromoethyl or β -chloropropyl group, is also essential to activity. The replacement of the chlorine or bromine by —OH or —O—R leads to complete inactivation for reasons mentioned below. Some quaternary derivatives of this series such as dibenzyl β -chloroethyl methyl ammonium methosulfate are also active.

In neutral or alkaline solutions the β -chloroethyl chain of these compounds closes with the amine nitrogen to form a highly reactive ethyleneimine ring which is then hydrolyzed to the inactive ethyl alcohol derivative with the release of HCl. Thiosulfate reacts rapidly with this ring to

form the ethyl thiosulfate derivative *in vitro*. Prior treatment of an animal with thiosulfate completely prevents the sympatholytic action, indicating that the same reactions occur *in vivo*, and that the ethyleneimine ring compound is probably the intermediate directly involved in the blocking. It is possible that substitutions on the benzyl group or its replacement alter the sympatholytic properties of these compounds by an inductive effect modifying the ring formation. [This investigation was supported by a grant from Givaudan-Delawanna, Inc.]

The prevention of epinephrine-cyclopropane cardiac irregularities in dogs with dibenzyl- β -chloroethyl amine. MARK NICKERSON and SCOTT M. SMITH (by invitation), and LOUIS S. GOODMAN, *Depts. of Pharmacology and Anesthesiology, Univ. of Utah School of Medicine, Salt Lake City, Utah* (Read by title). The ability of dibenzyl β -chloroethyl amine and related compounds to block the excitatory effects of epinephrine (see accompanying abstract) prompted a trial of their prevention of epinephrine-induced cardiac irregularities in dogs sensitized by cyclopropane.

After induction of anesthesia with intravenous sodium pentothal (15–25 mg/kg), dogs were maintained on a 30% cyclopropane–70% O₂ mixture (percentages read from Heidbrink flowmeters) administered by means of an endotracheal catheter with inflated cuff. Total flows of 1000 cc/min for the first 15 minutes and 500 cc/min thereafter were used, and the 3 liter rebreathing bag was completely emptied at frequent intervals. This procedure maintained a level of almost complete intercostal paralysis. The protective dose of 20 mg/kg dibenzyl- β -chloroethyl amine HCl was given intravenously.

After cyclopropane equilibration for 30 minutes, the standard test dose of 10 μ g/kg of epinephrine was injected intravenously over a 50 sec period. Electrocardiograms taken during and after these injections in control and treated dogs showed the following results:

	Control	Treated
No. of dogs	14	9
Death due to ventricular fibrillation	8 (57%)	0
*Ave. total period of irregularities	137 sec	4 sec
*Ave. period of ventricular tachycardia	97 sec	

* In dogs without ventricular fibrillation

The protected dogs showed a marked sinus tachycardia. Treated animals were also given 10 and 100 times the standard dose of epinephrine with only minor and brief cardiac irregularities. Dibenzyl β -chloroethyl amine afforded greater protection than did ergotamine or priscol. [This investigation

was aided by a grant from Givaudan-Delawanna, Inc.]

Effect of anti-reticular cytotoxic serum (ACS) on the healing of experimental wounds in rats MARK NICKERSON, THOMAS BURNS, and ARNOLD M. COOPER (introduced by Louis S. Goodman) *Dept. of Pharmacology, Univ. of Utah School of Medicine, Salt Lake City, Utah* (Read by title) Anti-reticular cytotoxic serum prepared by repeatedly injecting rabbits with rat spleen and bone marrow suspension possessed marked organ specificity showing a complement fixation titer for rat spleen and bone marrow antigen 5 to 10 times that for rat muscle antigen. Hemolysis content was negligible.

Rate of healing was measured by breaking and tensile strengths on the 9th day after skin and laparotomy incisions and fibular fractures. Beginning two days prior to the experimental trauma, injections of serum were given at 3-day intervals for three doses. Experimental animals (groups of 8 to 12) were given 0.25, 5, 40, or 600 units/kg (unit = ml serum \times titer) of ACS per injection. Controls received comparable amounts of normal rabbit serum.

Analysis of the data on 60 rats showed no significant differences between the rate of healing in the experimental and control series. However, the possible deleterious (blocking?) effect of large doses of ACS was shown by the fact that 3 of the 8 animals receiving 600 units/kg of ACS failed to survive the 9-day postoperative period. No deaths occurred in the control groups or in those receiving smaller doses of ACS.

Although the data reveal no stimulating effect of small doses of ACS on the healing process, such a possibility is not disproved. More sensitive and less variable tests may be required, or it may be that this effect cannot be demonstrated in normal animals but only in those animals whose healing mechanisms are not functioning efficiently. [This investigation was aided by a grant from Givaudan-Delawanna, Inc.]

Studies of the sympatholytic drug Dihydroxy-ergotamine (DHE 45) O. S. ORTH, *Dept. of Pharmacology, Univ. of Wisconsin Medical School, Madison* (Read by title) Several clinical reports have indicated that the synthetic sympatholytic drug dihydroxyergotamine (DHE 45—Sandoz) is as effective as ergotamine tartrate in the relief of migraine headaches. In addition, it does not produce the disturbing side-effects of other ergot preparations used for treating this condition.

In the present investigation it has been found that DHE 45 prevents cyclopropane-epinephrine cardiac effects in the dog if 0.4 mg of the drug per kilogram of body weight is administered before or with the epinephrine injections. This is approximately twice the amount of ergotamine tartrate

required for prevention of such arrhythmias. The protection lasts for about an hour. The compound does not produce an epinephrine reversal of the blood pressure in dogs anesthetized with nembutal, amytal, diethyl ether or chloroform. Instead there is an elevation of blood pressure when epinephrine is injected after DHE 45 has been administered in the dosage stated.

The absence of an oxytocic effect in the rat has been demonstrated by animals having intravenous injections of 5 and 10 mg/kg made daily during the entire gestation period. They bore normal litters and nurtured them successfully while the injections were continued.

In chronic toxicity studies in rats, 1.25 mg/kg of ergotamine tartrate administered intravenously each day routinely caused necrosis and a dry gangrene of the tip of the tail after only two to ten injections. Gangrene was rarely produced in another group of animals similarly treated with DHE 45, with injections of 5 and 10 mg/kg, for more than thirty days. Pathological changes in other organs from the action of each of these drugs are being studied.

The mechanism of action of chloroform on the heart O. S. ORTH and ROLAND R. LIEBENOW (by invitation) *Dept. of Pharmacology, Univ. of Wisconsin Medical School, Madison*. The general impression that the early toxic action of chloroform on the heart causes death by ventricular fibrillation arose from initial studies made on cats. Despite repeated disproof of this mechanism in other species, the idea still is retained by many individuals.

The present study concerning the effect of chloroform on the heart was done with dogs. Continuous electrocardiographic observation was made during the period of rapid, open-drop induction and through the various planes of surgical anesthesia until respiratory arrest was attained.

Cardiac arrhythmias frequently occurred. They were of various types with ventricular standstill or cardiac arrest being the most serious. Ventricular tachycardia and ventricular fibrillation were rarely if ever encountered. If, at the time of such arrest, the anesthetic administration was stopped and artificial ventilation with atmospheric air promptly initiated, the heart usually resumed a normal rhythm. Failure to recognize this early and extremely toxic action of the agent and immediately attempt to decrease its concentration in the tissues is believed to be the cause of early chloroform deaths. They are preventable and have been incorrectly interpreted as being due to ventricular fibrillation.

After such initial anesthetization, if an animal again was deliberately depressed to respiratory arrest, cardiac arrhythmias frequently did not recur unless there was an ensuing hypoxemia,

which *per se* will cause irregularities to be initiated. The effects of vagotomy, sympathetic denervation, the administration of epinephrine, and other procedures to determine the initial site of action of chloroform in causing cardiac disturbances will be presented.

The effect of phloridzin on the renal excretion of mercury S ANDERSON PEOPLES *Dept of Physiology and Pharmacology, Baylor Univ College of Medicine, Houston, Texas* In preliminary studies on mercury poisoning, we have found that 30 per cent of phloridzimized dogs are protected against the intravenous injection of 4 mg per kilogram of mercury as mercuric chloride, a certain fatal dose.

Since mercury specifically damages the cells of the proximal convoluted tubule of the kidney, it was thought that the phloridzin acts by preventing these cells from taking up mercury from the glomerular filtrate, preventing the accumulation of a toxic concentration of mercury in these cells, and increasing the rate of mercury excretion.

To test this theory, simultaneous mercury and inulin clearances were run in normal and phloridzimized dogs. Three normal dogs gave mercury clearances of 20, 22, and 30 cc/min/M² with corresponding inulin clearances of 58, 91, and 89 cc/min/M². Three phloridzimized dogs gave mercury clearances of 10, 9, and 12 cc/min/M² with corresponding inulin clearances of 135, 65, and 90 cc/min/M².

The lack of proportionality between the inulin and mercury clearances and the 60 per cent reduction in the mercury clearance after phloridzin indicate that our theory is incorrect. A more likely mechanism is that mercury is excreted almost entirely by the tubules and that phloridzin reduces the rate of mercury transport through the tubular cells. These cells apparently are able to carry mercury without injury up to a critical rate beyond which they are damaged.

If this assumption is correct, other substances interfering with tubular excretion should exert a protective action in mercury poisoning, and studies on benzoic acid, para aminohippuric acid and diodrast are under way.

Action of tetraethyl ammonium bromide on the superior cervical ganglion S A PEREIRA (by invitation) and G H ACHESON *Dept of Pharmacology, Harvard Medical School, Boston, Mass* The vasodepressor action of tetraethyl ammonium has been shown to be due to a blockage of vasoconstrictor nerve impulses at the autonomic ganglia (Acheson and Moe, in press). This blockage was analyzed in the superior cervical ganglion of the cat, using the contractions of the nictitating membrane as an indicator of ganglionic transmission.

Contractions produced by epinephrine, by stimulation of the post ganglionic nerves, or after

crushing the ganglion, by acetylcholine are unaffected by tetraethyl ammonium bromide injected intraarterially or intravenously. When the membrane and the ganglion are otherwise unstimulated, tetraethyl ammonium elicits only small contractions of the nictitating membrane in rather high doses. It does this whether the ganglion is intact or crushed.

During continuous stimulation of the preganglionic nerve, injections of tetraethyl ammonium cause temporary relaxation of the membrane, whose degree and duration increase with the dose (0.3 to 30 mg per kg intravenously). Except with the largest doses, this effect is repeatable. The stimulating action of acetylcholine on the ganglion is prevented by adequate doses of tetraethyl ammonium but that of potassium ion is not.

These results confirm previous findings that tetraethyl ammonium ion lacks muscarinic and anti-muscarinic actions. They also show that it has little nicotinic-stimulating action. The outstanding effect is a blockage of the ganglion similar to that produced by curare.

Quantitative studies on intradermal wheals II The use of a skin plethysmograph to study changes in the volume of cutaneous wheals C C PFEIFFER *Dept of Pharmacology of the Univ of Illinois College of Medicine, Chicago* Changes in the volumes of intradermal wheals made with physiological saline solution, Ringer's solution, solutions of various local anesthetics, and of various colloids have been followed by means of a skin plethysmograph. The curve of volume change is of value in determining wheal disappearance time and the inflammatory action to the dissolved chemical compounds. The instrument has also been used to measure the increases in volume of wheals produced by histamine diphosphate (1:1000). Under standard conditions of application of the histamine, the curves of increase in the volume of the wheals were constant from day to day in the same subject. The anti-histamine drug "Benadryl" given prophylactically in single doses of 100 mg orally produced a marked and characteristic decrease in the volume growth curve of the histamine wheals.

A study of the variables affecting the precision of the assay of estrogens L I PUGSLEY *Laby of Hygiene, Dept of National Health and Welfare, Ottawa, Canada* The slope of the regression lines were calculated from the data obtained after subcutaneous and oral administration of a number of estrogens showing that the subdivision of the doses, time of smearing and time of dosing were important factors in determining the precision of the biological assay of these substances.

Comparative toxicity and efficacy of "Urea Stibamines" in experimental leishmaniasis RACHAEL K REED, JOSEPHINE MAR AND HAMILTON

H ANDERSON¹ *Division of Pharmacology and Experimental Therapeutics, Univ of California Medical School, San Francisco* "Urea stibamine" was introduced by Brahmachari in 1922 as an effective pentavalent antimonial compound for the therapy of leishmaniasis. Since then a number of efforts have been made in the United States to synthesize this agent, which is of uncertain structure and of varying antimonial content.

Toxicity tests in mice of various lots of recent manufacture revealed marked differences in response. Intraperitoneal injection of Brahmachari's "urea stibamine" in inbred, starved, white mice indicated that this compound had an LD₅₀ of 404 ± 27 mg/kg. No significant signs of toxicity were noted. Congestion of the liver and peritoneum was observed in some animals. In one of several lots of an American product the LD₅₀ in mice was 266 ± 19 mg/kg. These animals showed marked protrusion of the eyeballs and hemorrhage into the ocular tissues. In some mice opacity of the cornea developed. Before death the respiration was slowed, and a flaccid paralysis of the hind legs occurred. Congestion of the lungs was observed postmortem.

For the treatment of experimental infections of *Leishmania donovani* in inbred, male, Syrian hamsters (*Cricetus auratus*) Brahmachari's compound was given to 5 animals in 6 daily intraperitoneal doses of 120 mg/kg (M.T.D.) each. A few LD bodies were found in Geimsa stained smears of splenic tissue, but subcultures in N.N.N. medium resulted in no growth. The American product, 142.5 mg/kg (M.T.D.) daily, given for 6 days, cleared 4 of 5 animals of their infection. In each series spleens appeared of average size.

The antimonial content of the Brahmachari preparation was 47.16%, while the American compound contained 43.0%. [The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Univ of California.]

Chemotherapy of plasmodium knowlesi infections in macaca mulatta monkeys. ARTHUR P. RICHARDSON, R. I. HEWITT (by invitation), L. D. SEAGER, M. M. BROOKE (by invitation), F. MARTIN, and H. MADDUX (by invitation). *Dept of Pharmacology, Univ of Tennessee, Memphis, Division of Pharmacology, The Squirb Inst for Medical Research, New Brunswick, N. J.* Intravenous injection of 50 million parasitized cells per kilo produced infections in *Macaca mulatta* monkeys comparable to those ordinarily used in chemotherapeutic studies with avian malaras. Two observations were used as criteria of effect of drugs: a) per cent mortality within

ten days after inoculation, b) highest of daily parasite counts up to and including the tenth day after inoculation. Drugs were administered at eight hour intervals beginning 15 hours after inoculation and continuing for five days. Under these standardized conditions sulfadiazine was found to be approximately 175 times as active as quinine in suppressing this infection. Delaying treatment for 72-80 hours had little effect on the dose of sulfadiazine or quinine required to save infected animals. The chemotherapeutic effect of sulfadiazine was effectively antagonized by concomitant administration of para amino benzoic acid. We have confirmed the observations of others that sulfonamides effect a radical cure of this infection. [The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Univ of Tennessee.]

Absence of significant changes in blood coagulability during digitalization. JAMES A. RICHARDSON (by invitation) and R. P. WAITON. *Dept of Pharmacology, Medical College of South Carolina, Charleston*. Thrombus formation and embolization following digitalis administration have been attributed to a claimed increase in blood coagulability produced by digitalization. Our experiments fail to support any claims that digitalis preparations significantly affect blood coagulation time in dogs and are in essential agreement with two more recent reports presenting similarly negative results (Fed. Proc. 4: 132, 136, 1945). The conditions of our present experiments have been described in a previous examination of reputed anti-coagulant drugs (J. P. E. T., 72: 146, 1941). Digitalis preparations were administered by the intramuscular injection of ampouled, proprietary solutions in doses of $\frac{1}{2}$ to $\frac{3}{4}$ cat units per kg, the most usual dose being $\frac{1}{2}$ unit of Digifolin per kg. Coagulation time of venepuncture samples was determined over periods up to 4 hours following the drug injection. In 10 dogs, the average pre-digitalis coagulation time was 5.78 min (S.D. of .57 min with 20 detns), the average post-digitalis coagulation time was 5.01 min (S.D. of 1.04 min with 40 detns). This extent of decrease in coagulation time is no greater than that obtained in previous experiments without digitalis, it may be attributed, for instance, to the effects of the anesthetics used (pentobarbital and amytal) or to the production of thromboplastic substances through repeated venepunctures. Nine experiments with doses of 0.1 and 0.2 mg/kg of heparin intravenously gave no evidence that digitalization affected the typical course of heparin effects. The *in vitro* addition of stock solutions of digitalis preparations to drawn blood in a ratio of 1 to 5 had no important effect on coagulation time.

The mechanism of action of prostigmine

¹ With the technical assistance of Elsa M. Zitoer

WALTER F RIKER (by invitation), W CLARKE WESCOE (by invitation), McKEEN CATTELL, and EPHRAIM SHORR *Depts of Medicine and Pharmacology, Cornell Univ Medical College and The New York Hospital, New York City* It has been suggested by others that prostigmine produces cholinergic effects in addition to its inhibition of cholinesterase The structural formula of this agent reveals it to be an analogue of both the natural and synthetic choline esters Since the pharmacological effects of all these substances are similar, the possibility was entertained that there might be a common chemical action for all, rather than an entirely different mode of action for prostigmine

The inactivation of muscle cholinesterase by di-iso-propyl fluorophosphate has provided unique experimental conditions for the exploration of this concept Under these circumstances any cholinergic effect would be attributable to an action other than that arising through cholinesterase inhibition Utilizing the intact cat gastrocnemius, muscle cholinesterase activity was destroyed by the intra arterial injection of di iso propyl fluorophosphate At this time, the responsiveness of the muscle was tested to the intra arterial injection of acetylcholine, carbamyl choline and prostigmine Similar contractile responses were obtained with all three, from which it was inferred that prostigmine acts on the effector cell in similar fashion to the true choline esters

It is of further interest that the other property of prostigmine, namely cholinesterase inhibition, is also shared by the synthetic choline esters, as is particularly evident with therapeutic amounts of carbamyl choline in man

A further similarity between the action of prostigmine and the choline esters has been found in the curarization of cat muscle by prostigmine This observation may have clinical implications for the optimal use of prostigmine in myasthenia gravis [*The work described in this paper was carried out under a contract between The Chemical Warfare Service, U S Army and Cornell Univ Medical College*]

Dose and intensity of action and elimination of prostigmine M A ROOR (introduced by O KRAYER) *Dept of Pharmacology, Harvard Medical School, Boston, Mass* Further experiments (Friend, D and O Kraye, J Pharmacol and exper Therap, 72 15, 1941) have been conducted following the serum cholinesterase activity (determined by the Warburg manometric technique) in dogs and man Single oral doses and intravenous infusions were given in anesthetized dogs and in man As was found with physostigmine (Kraye, O, A Goldstein, and F Plachte, J Pharmacol and exper Therap, 80 8, 1944) on continuous infusion, as the intensity of the inhibition in-

creases much greater amounts of prostigmine must be given to produce a further increase in esterase inhibition (Kraye, O, J Nervous and Mental Diseases, 100 617, 1944) This effect is most marked with doses less than 1 microgram per kilogram per hour and greater than 10 micrograms per kilogram per hour In all experiments constant levels of cholinesterase inhibition were reached and maintained Recovery of cholinesterase activity began immediately upon cessation of the infusion Inhibition established by continuous infusion was intensified by tying off the kidneys, confirming (Friend, D and O Kraye, J Pharmacol and exper Therap 72 15, 1941) that part of the elimination of prostigmine proceeds via the kidney Infusion into the portal system leads to a lesser degree of inhibition than infusion into the femoral vein, indicating that part of the destruction of prostigmine proceeds in the liver

Oral administration of prostigmine to dogs produces maximal inhibition of cholinesterase activity in from 1 to 4 hours Identical doses in the same dog produced widely divergent degrees of cholinesterase inhibition Recovery to normal cholinesterase activity proceeded at about the same rate in each experiment

Continuous infusion of prostigmine in patients with myasthenia gravis has produced levels of cholinesterase inhibition in from 3-5 hours The dose response curve appears to be moved to the right in man as compared with dogs

On the permeability of the nerve axon to diisopropylfluorophosphate M A ROTHENBERG AND D NACHMANSOHN (introduced by H T Clarke) *Depts of Neurology and Biochemistry, College of Physicians and Surgeons, Columbia Univ, New York* Experimental evidence indicates that the release of acetylcholine is closely associated with the nerve action potential It may be assumed that the ester depolarizes the nerve membrane by rendering it permeable to all ions and thus permits flow of current The function of cholinesterase is then the inactivation of the ester leading to rapid restoration of the polarized state of the membrane

In agreement with this concept, it has been shown in experiments on the giant axon of squid that conductivity is rapidly abolished if the axon is kept in eserine and the acetylcholine released is thus protected against the action of cholinesterase (Bullock, Nachmansohn, and Rothenberg) The effect is easily reversible in agreement with the well known reversibility of the enzyme inhibitor complex Prostigmine, on the other hand, which, like acetylcholine, is a quaternary ammonium salt has no effect on the nerve action potential, because such compounds cannot permeate the lipid membrane In view of the strong anticholinesterasic effect of diisopropylfluorophosphate

(DFP) its effect on conductivity has been tested in collaboration with T H Bullock. The purpose was to test the permeability of the nerve membrane to DFP and the reversibility of the enzyme inhibitor complex.

It was found that the action potential is reversibly abolished. The data obtained so far will be presented and discussed.

Differentiation between the effects of DFP and eserine may be obtained by studying their action on the electrophoresis of pure cholinesterase. Pure enzyme has been prepared by fractionate ammonium sulphate precipitation and, in collaboration with K G Stern, by ultracentrifugation.

The response of "fatigued" myocardium to known concentrations of a cardiac glycoside. WILLIAM T. SALTER and (by invitation) WALLACE F. WHITE, *Dept of Pharmacology, Yale Univ School of Medicine*. Isolated papillary muscles from right ventricles of cat hearts were electrically stimulated at a uniform rate in order to "fatigue" them. They were then treated with a series of known concentrations of a cardiac glycoside and the response determined by measuring the height of isometric contractions. Fresh muscles failed to respond to relatively high concentrations of ouabain. The greater the "fatigue," the lower was the concentration needed to evoke a response. Concentration-response curves were linear when log concentration of ouabain was plotted against millimeter contraction of a single muscle. This linear response provides a means of determining threshold ($1 \mu\text{g}\%$), maximal ($10 \mu\text{g}\%$), and toxic ($20 \mu\text{g}\%$) concentrations of ouabain and other cardiac drugs on the same muscle.

Various types of "fatigue" were tried. Muscles were "fatigued" by modifying the fluid medium. Krebs-Henseleit modified Locke's solution would not permit these muscles to become "fatigued" for days but when phosphate buffer was substituted for carbonate buffer they declined rapidly. Hypoxia was not suitable for "fatiguing" because improvement by drugs was not possible without introducing oxygen. Small amounts of serum and changes in the concentration of certain ions were also effective. Muscles kept under adverse conditions too long became irreversibly unresponsive. [Grant from the Fluid Research Fund.]

A method for the assay of adrenocorticotrophic hormone. MARION A. SAYERS and GEORGE SAYERS (introduced by Louis S. Goodman) *Dept of Pharmacology, Univ of Utah School of Medicine, Salt Lake City*. The relationship which exists between the concentration of ascorbic acid in the adrenal and the adrenocorticotrophic activity of the anterior pituitary has been used as a basis for the assay of pituitary adrenocorticotrophic hormone (A.C.T.).

Male rats, 100 to 125 grams in body weight, were hypophysectomized. Eighteen to 24 hours later the

left adrenal was removed under sodium pentobarbital anesthesia and analyzed for ascorbic acid. A solution of the material to be assayed was then injected intravenously. One hour after the beginning of the injection the right adrenal was removed and analyzed for ascorbic acid. The reduction in adrenal ascorbic acid, expressed as the difference between the content of this substance in the left and right adrenals, is proportional to the amount of A.C.T. injected. Doses of purified A.C.T. equal to 10, 5 and 2.5 micrograms per 100 grams of body weight produced respectively decreases in adrenal ascorbic acid of 20 ± 13 , 163 ± 27 and 133 ± 9 milligrams per 100 grams of tissue.

The method is being applied to the assay of A.C.T. in certain body tissues and fluids. [Aided by a grant from the Utah Copper Company Research Fund, Univ of Utah School of Medicine.]

Regulation of pituitary adrenocorticotrophic activity. GEORGE SAYERS and MARION A. SAYERS (introduced by Louis S. Goodman) *Dept of Pharmacology, Univ of Utah School of Medicine, Salt Lake City*. Adrenal ascorbic acid decreased from 419 ± 7 to 273 ± 11 milligrams per 100 grams of tissue following exposure of rats to $3^{\circ}\text{--}5^{\circ}\text{C}$ for one hour. This decrease was shown previously to be due to increased elaboration of adrenocorticotrophic hormone from the pituitary. Administration of cortical extract one hour previous to the beginning of exposure inhibits pituitary adrenocorticotrophic activity. A relationship exists between the dose of cortical extract and the degree of inhibition. Subcutaneous injection of 0.2, 0.1, and 0.01 ml of cortical extract (Upjohn) per 100 grams of body weight resulted respectively in the following levels of adrenal ascorbic acid, 406 ± 19 , 347 ± 30 and 287 ± 25 milligrams per 100 grams of tissue. The minimum effective inhibitory dose (M.E.I.D.) of cortical extract under these conditions lies between 0.1 and 0.2 ml per 100 grams of body weight. The M.E.I.D., expressed as micrograms per 100 grams of body weight, is 50–200 for corticosterone and 200–400 for desoxycorticosterone. One milligram of progesterone had no inhibitory effect. Therefore, replacement of OH on C_{11} with H causes considerable loss of activity. The OH on C_{11} appears to have slight influence upon activity.

It has not been definitely established whether cortical hormones act directly or indirectly through metabolic changes to inhibit the elaboration of pituitary adrenocorticotrophic hormone. However, the fact that corticosterone and desoxycorticosterone differ considerably in their metabolic activity and yet have approximately the same inhibitory potency on the pituitary suggests that these compounds act directly on this gland. [Aided by a grant from the Utah Copper Company Research Fund, Univ of Utah School of Medicine.]

The action of 1, 1-diphenyl-1-(dimethylaminoisopropyl)-butanone-2, a potent analgesic agent CHARLES C SCOTT and K K CHEN *Lilly Research Labys, Indianapolis* The compound as given in the title was tested for a number of pharmacologic reactions. Its analgesic effect in rats (Haffner technic), dogs, and humans (Wolff-Hardy method) is approximately equal to morphine. Other actions of this substance resemble those of morphine, but there are also distinct differences. Similar effects are as follows. In analgesic doses, it produces marked respiratory depression in dogs with or without anesthesia. Heart rate may be slowed to 30 per minute, slowing being mainly vagal. Salivary secretion is stimulated in the unanesthetized dog, but is slightly depressed in anesthetized animals. Mice show typical Straub reaction and rats develop postural rigidity. In contrast to morphine, the product has a weak antispasmodic action on the isolated gut and in unanesthetized dogs, an absence of emetic action in dogs, and a much weaker stimulating effect in cats. Dogs do not appear to develop tolerance to its analgesic action. Toxicity studies (LD_{50} in mice and feeding experiments in rats) have been carried out. No effect was noted on red or white blood cells of rats or dogs during 28 consecutive days of medication. In man, the drug in 5 mg doses, orally, is an effective analgesic, being readily absorbed by this route and partially excreted in the urine. This dose produces little or no effect on heart rate and respiration. Slight lightheadedness may result from this amount, but euphoria apparently does not occur. Clinical trials are warranted.

Insulin resistance in owls CHARLES C SCOTT and K K CHEN *Lilly Research Labys, Indianapolis* Effect of intravenous injections of insulin on blood sugar was studied in 9 horned owls (*Bubo virginianus*). A stock solution of insulin containing 500 units per cc was used. Doses varied from 2 to 4000 units per kg. They uniformly caused a fall of blood sugar. Hypoglycemia was not always proportional to the amount of insulin administered. The results of small and large doses differed in duration of hypoglycemia, primary hyperglycemia, and lethal action. Injections of 2 to 32, 64 to 512, and 1000 to 4000 units per kg caused a hypoglycemic action of 8, 18, and 119 hours' duration, while the mean lowest blood sugar in each group was 113, 124, and 71 mg per cent, respectively. Doses of 64 to 512 units per kg produced a primary hyperglycemia, the average rise in blood sugar being 38 mg per cent and lasting an hour. Primary hyperglycemia following 1000 to 4000 units per kg amounted on the average to 65 mg per cent and lasted 4 hours. The hyperglycemic action was not due to impurities in regular insulin, since identical results were obtained with crystalline insulin. Doses of 1000 to 4000 units per kg caused death in

4 of 11 tests, the hypoglycemia being more severe in those owls that died. No convulsions occurred at any time, even with extreme prolonged hypoglycemia with blood sugars as low as 13 mg per cent. There was prostration during hypoglycemia.

The acute and chronic toxicity of stilbamidine LLOYD D SEAGER and GINA CASTLENUOVO (by invitation) *Depts of Pharmacology and Anatomy, Woman's Medical College of Pennsylvania* Mice given 100 mg /kg orally of stilbamidine daily for 120 days, showed some fatty metamorphosis of the liver and in some instances marked degeneration of the renal convoluted tubules. No evidence of damage was found in other organs. Cloudy swelling and slight tubular degeneration in the kidney were found in mice receiving 10 mg /kg daily for a week. Distension of central veins, sinusoids and often of the interlobular veins was an invariable feature in all the experiments.

Rabbits injected subcutaneously with 50 mg /kg or over usually die in one to ten days. They show loss of appetite, weight and weakness. Sometimes diarrhoea is a prominent feature. Rabbits treated with 10 mg /kg daily all die before the tenth dose. In rabbits receiving 100 mg /kg convulsions and death occurred in a few days. These symptoms and death are attributed to a fall in blood pressure. One group of animals treated with 25 mg /kg once a week survived for four to five weeks. The most marked tissue changes were seen in the last group. Striking fatty metamorphosis of the liver and extensive tubular degeneration in the kidney with some involvement in the glomeruli was noted. The central vein and sinusoids in the liver were very distended. A prominent feature of toxicity seen in rabbits but not in mice is a delayed effect. [This investigation was made with the assistance of a grant from the Committee on Therapeutic Research, Council on Pharmacy and Chemistry of the American Medical Association. The stilbamidine used was supplied by Merck and Co.]

The antipyretic action of camphor KATHLEEN G W SEYMOUR (by invitation) and ELDON M BOYD *Dept of Pharmacology, Queen's Univ, Kingston, Canada* The internal use of pharmaceutical preparations of camphor was formerly a common procedure in the symptomatic treatment of fever. Modern textbooks of pharmacology still contain reference to the reputed antipyretic action of camphor, some noting that it is used as a home "remedy" for fever. No recent research has been done upon the subject. Hence camphor was given parenterally and by stomach tube in a wide range of doses to some 500 animals (albino rats, guinea-pigs, rabbits and cats) with an artificial fever produced by injection of peptone. Phenazone, used as a control, caused a return toward normal of the febrile temperature, but camphor had either no or a very feeble antipyretic effect. Camphor had no

effect upon normal body temperature. Neither was camphor antipyretic, to any degree, in natural fever caused by infection of several rabbits, albino rats, guinea-pigs and cats. For parenteral use, camphor dissolved in oil was given and for stomach tube administration, spirit of camphor, and the dose ranged from small doses up to those which, in cats, produced convulsions. It was concluded that camphor has little or no antipyretic action.

Pharmacological studies of anti-histamine compounds. T. R. SHERROD, H. F. SCHOMMER and E. R. LOEW (introduced by C. C. Pfeiffer), *Dept of Pharmacology, Univ of Illinois College of Medicine, Chicago*. The anti-histamine compounds, β -dimethylaminoethyl benzhydryl ether HCl (Benadryl), N-p-methoxybenzyl-N-dimethylaminoethyl α -aminopyridine HPO₄ (2786 RP), and its homologue, N-benzyl-N-dimethylaminoethyl α -aminopyridine HCl (63-C or Pyribenzamine) were administered intravenously in doses of 3 mg/kg to intact dogs anesthetized with pentobarbital sodium. Respiration was stimulated, especially by the latter two drugs. After a slight initial fall each drug raised the blood pressure about 10 mm Hg for several minutes following injection.

Benadryl diminished the depressor action of histamine and acetylcholine, augmented the pressor action of epinephrine, decreased duodenal motility and had no effect on uterine activity.

Compound 2786 RP (Bovet and Walthert, 1944) is also a potent anti-histamine compound in that it diminished the depressor effect of histamine. The pressor action of epinephrine was enhanced. Unlike Benadryl, 2786 RP stimulated uterine and duodenal activity and did not inhibit the depressor action of acetylcholine.

Under the conditions of the experiment no significant quantitative or qualitative differences between 2786 RP and its homologue, Pyribenzamine (Mayer et al, 1945) could be demonstrated.

It is concluded that the three anti-histamine drugs diminish the depressor effects of histamine and potentiate the pressor action of epinephrine in the anesthetized dog. In addition to inhibiting the spontaneously active duodenum, Benadryl antagonizes the spasmogenic effects of histamine and acetylcholine. In contrast, both of the α -aminopyridine compounds stimulate the duodenum and uterus and do not inhibit the depressor action of acetylcholine.

The adenosinetriphosphatase activity of smooth muscle. HARON O. SINGER and NATHAN MILLMAN (introduced by R. A. Woodbury), *Physiology and Biochemistry Division, Ortho Research Foundation, Linden, N. J.* The adenosinetriphosphatase activity of various organs with nonstriated muscle component was studied. A comparison was made of the activity in the uterus of rats and rabbits. The relationship between enzymatic activity

and the stage of estrous cycle in rats was investigated. The effects of additions of chemical mediators such as acetylcholine and epinephrine and of smooth muscle depressants and stimulants such as the posterior pituitary oxytocic principal were examined.

The modifying action of neostigmine on pain threshold responses to various opiates. DONALD SLAUGHTER, *Dept of Physiology and Pharmacology, Southwestern Medical College, Dallas, Texas*. Sometime ago, we reported that in human subjects neostigmine enhanced the analgesic action of the usual therapeutic doses of morphine, when tested by a modified Wolff-Hardy-Goodell pain threshold apparatus, to the extent that approximately one half the amount of morphine plus neostigmine would be as effective as twice that amount of morphine alone. Further studies, comprising 293 experiments on 61 subjects, indicate that neostigmine (0.5 mg) potentiates the analgesic effects of "Dilaudid," "Pantopon," and codeine, when administered together subcutaneously. The effectiveness of one half of the doses (3, 10, and 32 mg, respectively) of the above-mentioned opiates plus neostigmine is equal to approximately the effects of twice the dose (6, 20, and 64 mg, respectively) of these opiates administered alone. With respect to codeine, the effect of the combination is greater than twice one half the dose. In addition to the above experiments, the analgesic actions of monoacetyl morphine were studied. Results show that a single dose of 4 mg of this opiate was as effective as 16 mg of morphine sulfate. However, monoacetyl morphine was not enhanced by neostigmine.

It has been argued that potentiation of morphine analgesia by neostigmine was not valid since the half doses of opiates used increased the pain threshold response when administered alone. However, 4 mg of morphine alone produced only a slight change in the pain threshold response, but when combined with neostigmine the analgesic effect was markedly enhanced. [This work was made possible by a grant-in-aid from Hoffmann-La Roche, Inc., Nutley, New Jersey.]

Studies on Bromaspirin. DONALD SLAUGHTER, JABEZ GALT and JANE C. NEFF, *Dept of Physiology and Pharmacology, Southwestern Medical College, Dallas, Texas* (Read by title). A modified Wolff-Hardy-Goodell apparatus was used to test the effect of "Bromaspirin" (5-Bromoacetylsalicylic Acid) on pain thresholds in man. These results were compared with similar dosages of acetanilid. A total of 32 experiments were performed on 9 subjects. Dosages used were 0.15 gram, 0.3 gram, and 0.6 gram, of acetanilid and "Bromaspirin," respectively. The maximal effects of acetanilid and "Bromaspirin" were reached 30 minutes and 45-60 minutes, respectively, following

oral administration. It was concluded from the results of these pain threshold responses that "Bromaspirin" is twice as effective in its analgesic properties as acetanilid. In addition, there were no untoward reactions from the "Bromaspirin," whereas acetanilid, especially at a 0.6 gram dosage, provoked various unpleasant manifestations.

Acute toxicity experiments now in progress indicate that "Bromaspirin" has approximately the same LD₅₀ as aspirin. Further data on acute, as well as chronic, toxicity experiments will be reported at a later date. [This work was made possible by a grant-in aid to one of us (D. S.) from Dr. James C. Munch, Upper Darby, Pennsylvania.]

Determination of salicylate fractions in urine following the administration of salicylates. PAUL K. SMITH and HELEN L. GLEASON, *Dept. of Pharmacology and Biochemistry, AAF School of Aviation Medicine, Randolph Field, Texas*. (Read by title.) Estimations of the free salicylate, salicyluric acid and total salicylates were made in urine by colorimetric methods similar to those of Brodie, Udenfriend, and Coburn (J. Pharmacol., 86: 114-17 (1944)) for plasma. Dilute urine was extracted with ethylene dichloride and the color formed with iron measured as in the plasma method. A similar procedure using carbon tetrachloride instead of ethylene chloride was carried out. From standard solutions it was shown that pure salicyluric acid gave 0.82 of the color given by an equimolecular quantity of salicylic acid and that ethylene chloride extracted 0.90 of the salicylate and 0.73 of the salicyluric acid while carbon tetrachloride extracted 0.92 of the salicylic acid and 0.05 of the salicyluric acid. From this data the amounts of salicyluric acid and salicylic acid in urine samples could be calculated. Total salicylate was determined by heating dilute urine on the steam bath with concentrated hydrochloric acid and estimation of the salicylate color. Under the conditions of the method only one third of the salicyluric acid was hydrolyzed and a small correction was made for the unhydrolyzed portion.

This method, of course, does not take into account the fractions not containing salicyl radicals, as described by Kapp and Coburn (J. Biol. Chem. 145: 549, 1942).

It has been determined that chloroform instead of ethylene dichloride can be used for plasma determinations.

Studies on the pharmacology of salicylates. PAUL K. SMITH, HELEN L. GLEASON, CHARLES B. STOLL and S. ORGORZALEK, *Dept. of Pharmacology and Biochemistry, AAF School of Aviation Medicine, Randolph Field, Texas*. The metabolism of salicylates was studied in both rheumatic fever and other patients. Plasma levels of salicylate were done by the method of Brodie, Udenfriend and Coburn (J. Pharmacol. 80: 114-17 (1944)). Urinary fractions of free salicylate, salicyluric acid and total salicylate

were done by methods devised in this laboratory.

It was demonstrated that the administration of ammonium chloride resulted in more sustained plasma salicylate levels while the administration of sodium bicarbonate was associated with much lower levels, in confirmation of the observations of Smull, Wegria, and Leland (J. Am. Med. Assoc. 125: 1173-75 (1944)). The effect of the acid or alkaline salts on the excretion of salicyluric acid or salicyl glycuromides was very small, but there was a large increase in the excretion of free salicylate when sodium bicarbonate was given. There was a marked dependence of renal clearances of free salicylate on the urinary pH, with a sharp increase above pH 7.0.

Most of the salicylate in human plasma is bound to the non-diffusible components, presumably plasma proteins. The amount bound *in vitro* is similar to the amount bound *in vivo*. Even at high plasma salicylate concentrations very little salicylate concentrations very little salicylate is in the erythrocytes.

After the oral administration of aspirin the only detectable form of salicylate in the plasma is free salicylate. When aspirin, freshly neutralized with sodium bicarbonate, was given intravenously to dogs plasma samples taken one hour later revealed only free salicylate.

The pharmacologic action and metabolism of a series of compounds chemically related to DDT. M. I. SMITH, H. BAUER (by invitation), E. F. STOHLMAN (by invitation) and R. D. LILLIE, *Division of Physiology and the Pathology Lab., National Inst. of Health, Bethesda, Md.* The acute toxicity in rats, the chronic toxicity and microscopic pathology in rabbits, and the metabolism in rabbits were studied in a series of twelve compounds structurally related to DDT (p,p'-dichloro diphenyl trichloroethane). Some of the compounds had no halogen in the molecule, several had chlorine in the benzene nucleus only, others had chlorine in the ethane group only, two of the compounds were partially dechlorinated in the aliphatic chain, and one of the compounds differed from DDT by having bromine replacing the chlorine in the benzene nucleus. The results of the study permit the following conclusions:

- 1 The characteristic neurotoxic and hepatotoxic actions of DDT are dependent on five halogens in the molecule.

- 2 Compounds with either aromatic or aliphatic halogen alone, and compounds partially dechlorinated in the ethane group are much less toxic than DDT. They exhibit little or none of the central nervous system actions of DDT.

- 3 Two of the compounds, the partially dechlorinated p,p'-dichloro diphenyl dichloroethane and the bromine analogue of DDT, are degraded like DDT and excreted in the urine as the acetic acid

derivative, while all the others studied have yielded excretory products in the urine which when examined spectrophotometrically by the method of Schechter and Haller (Jour Am Chem Soc 66 2129, 1944) were indistinguishable from

		LD ₅₀	CNS	LN	MA M μ	
					In vitro	In vivo
DE			0	0	0	0
DK					0	0
DA			0	0	620	620
DT		1.5	0	0	0	0
DDM		1.0	0	+	520	520
DDE		1.0	0		520 540	
DDK			0	+	540	540
DDK ₁			0	+	500	500
DDA		2.0	0	0	540	540
DDD ₁		1.0	+	0	540	540
DDD		2.7	0	+	600	540
DDT		0.15	+++	+++	600	540
DBrDT		0.15	+++	+++	600	540

the compounds themselves, and they are presumed to be excreted unchanged

The accompanying chart shows the structure of the compounds, the LD₅₀ for rats, the effects on the central nervous system (CNS) and extent of liver necrosis (LN) in rabbits, and the absorption maxima on spectrophotometric examination of the

nitration products of the compounds themselves (In vitro) and of the excretory products in the urine of rabbits (In vivo)

The influence of streptomycin and promin on the proliferation of tubercle bacilli in the tissues of the albino rat M I SMITH, WM T McCLOSKEY and E W LAMMART (by invitation) *Division of Physiology, National Inst of Health, Bethesda, Md* Four groups of rats, twelve each, were inoculated intraperitoneally with 2.5 mg tubercle bacilli, human strain A27 and treated as follows

A 50,000 units streptomycin per kg intramuscularly per day, and 0.75% promin (sodium p,p'-diaminodiphenylsulfone-N N'-dextrosesulfonate) in the diet for 36 days

B 0.75% promin in the diet to termination of experiment

C 50,000 units streptomycin as in A, and no promin, for 36 days

D Untreated controls

At 28 to 53 days after inoculation the animals were killed in equal numbers in each of the four groups and the tissues examined for the presence, viability, and pathogenicity of tubercle bacilli by (a) direct smears and Ziehl-Neelsen stain, (b) inoculation of lung suspensions on glycerine egg slants, (c) inoculation of lung suspensions subcutaneously in guinea pigs. Analysis of the data showed all the controls and all the animals of the promin group harboring viable pathogenic bacilli, while 8% of the streptomycin group and 42% of the combined treatment group were free from bacilli. These results confirm and extend the previously reported synergistic action of streptomycin and promin in the chemotherapy of experimental tuberculosis infection in guinea pigs (Smith and McClosky Pub Health Rep 60 1129, 1945)

Further observations on the action of sulfones in experimental tuberculosis. Chemical constitution and chemotherapeutic action M I SMITH, E L JACKSON (by invitation) and WM T McCLOSKEY *Division of Physiology, National Inst of Health, Bethesda, Md* Four new sulfones were tested for chemotherapeutic activity in comparison with promin (sodium-p,p'-diamino-diphenylsulfone N, N' dextrose sulfonate) in experimental tuberculosis in guinea pigs. The compounds were

- 1 4-4'-diamino-2-sulfamylidiphenylsulfone
- 2 Phenyl-n-propyl sulfone
- 3 4-amino 4'-hydroxylaminodiphenylsulfone
- 4 N - (p - aminobenzenesulfonylphenyl) - B - alanine

Compounds 1 and 4 were completely inactive. Compounds 2 and 3 showed some retardation of the tuberculous process, but the effect was much less and their toxicity considerably greater than that of promin. The results of this study appear to indicate (1) that carboxyalkyl or hydroxyl substit-

exists a linear relationship between the rate and the amount of substance oxidized. The oxidation proceeds at a constant rate throughout the entire process, and, therefore, the rate of oxidation is proportional to the amount of substance oxidized. The rate of oxidation is also proportional to the amount of substance oxidized. The rate of oxidation is also proportional to the amount of substance oxidized.

Depletion of oxidant-reductant alkaline solutions of methylene blue and orange. Potassium Selenate by Simmons. *School of Medicine, University of Utah*. When certain organic reducing agents are added to methylene blue or orange, the color of the solution changes. Upon heating to boiling, the color of the solution fades. It is regained when the solution is cooled and shaken. Upon standing the color is lost and can be regained by further shaking. All the solutions of organic reductants exhibit the same phenomenon, but are generally more sensitive and have a more rapid color return.

To test for the amount of oxygen necessary to return the color to a stable state with alkaline methylene blue a strong oxidizing agent was used. It was found that the amount of oxidizing agent used was related to the temperature and to the degree of alkalinity. Greater alkalinity and higher temperatures required greater amounts of oxidizing agent. No relationship was established between the reducing agent and the amount of oxidizing agent used.

The reducing agents used were dextrose, xylose, maltose, ascorbic acid and uric acid. The oxidizing agent used was potassium persulfate. The dyes were dissolved in potassium hydroxide and sodium carbonate.

The effects of body water and electrolyte shifts on experimental convulsions. EVERT A. SMITH, JR., JAMES E. P. TOMAR, and LOUIS S. GOODMAN. *Dept. of Pharmacology, University of Utah School of Medicine, Salt Lake City*. Effects of body water and electrolyte shifts on electroshock and drug-induced convulsions in rats were quantitatively analyzed. Extracellular fluid volume alterations without changes in electrolyte concentration did not change seizure thresholds or patterns. Acute increases in cellular fluid volume produced to an equal degree (14%) either by water orally or extracellular electrolyte depletion (ascular glucose up) reduced seizure thresholds more than 50%. Several lines of evidence indicated that lowering of seizure thresholds was related more to cellular swelling than to reduced electrolyte concentration. The critical increase in cellular fluid volume for spontaneous seizures was calculated to be approximately 10%.

Rats with cellular hydration produced by extracellular cation depletion had greatly reduced

thresholds for spontaneous convulsions. The effects of extracellular cation depletion on the threshold of water (NaCl) and potassium (KCl) were also studied. Extracellular cation depletion did not change the threshold of spontaneous convulsions in rats administered a non-convulsant dose of pentobarbital.

The pattern of maximal electroconvulsive therapy (MECT) and post-convulsive effects were analyzed in rats with cellular swelling. It was found that the pattern and metabolic activity were changed to threshold.

Seizure thresholds were also analyzed in extracellular cation depletion. A low potassium normal, rapid return resulted from restoration of extracellular cation (20% NaCl, 10% KCl). Normal extracellular cation thresholds were elevated by acute cellular dehydration (20% NaCl, 10% KCl) and water deprivation for 48 hours was without effect.

Phenobarbital, thiopental and diazepam had no effect on seizure thresholds. Quantitative studies of alteration in cellular and extracellular water and electrolyte patterns are being continued and correlated with changes in seizure properties. *Supported by a grant from the Research Fund, University of Utah School of Medicine, Salt Lake City, Utah*

Laboratory assay of anticonvulsant potency of some hydantoins. EVERT A. SMITH, JR., JAMES E. P. TOMAR, and LOUIS S. GOODMAN. *Dept. of Pharmacology, University of Utah School of Medicine, Salt Lake City*. (Received by title. Seven new hy-

Derivatives of Diphenylhydantoin	Toxic dose (mgm/kg, i.p.)		Protective Index	Change in initial electroshock threshold	
	1st dose	2nd dose		1st dose	2nd dose
5-ethyl-5-methyl	25	5	12	1.5	1.5
5-isopropylmethyl	25	5	12	1.5	1.5
5-phenyl	25	5	12	1.5	1.5
5-sec-butylmethyl	25	5	12	1.5	1.5
5-sec-propylmethyl	25	5	12	1.5	1.5
5-benzylmethyl	25	5	12	1.5	1.5
5-sec-butylmethyl	25	5	12	1.5	1.5
5-sec-propylmethyl	25	5	12	1.5	1.5

* Diphenylhydantoin (dihydantoin)

All compounds except the 5-ethyl, 5-methyl derivatives were kindly supplied by Dr. L. M. Long, Parma, Ohio and Co.

* Kindly supplied by S. M. Foss, Sandoz Chemical Works, Inc.

derivative was assayed in rats by two new laboratory techniques and compared with diphenylhydantoin. All compounds were administered i.p. The toxic dose (TD) was taken as that just causing

observable neurological deficit or other untoward effect. The protective dose (P) was that just required to abolish tonic extensor components of maximal electroshock seizures produced by current intensities five times threshold (Offner 60-cycle alternating current apparatus, Spiegel corneal electrodes, 150 mA, 0.2 sec stimulation). Cellular hydration lowered electroshock seizure threshold by more than 50% and was produced by acute extracellular electrolyte depletion (isosmolar glucose, 1 p). Hydrantoinates ineffective in elevating normal electroshock seizure threshold frequently elevated toward normal the experimentally lowered thresholds. The results obtained are shown in the accompanying table. Details of the two assay techniques employed here are being published in full. Correlation of laboratory data with clinical efficacy remains to be determined.

Depression of metabolism and temperature in traumatic shock as evidence of a toxic factor. HERBERT TABOR (by invitation) and SANFORD M. ROSENTHAL, *Division of Physiology, National Inst of Health, Bethesda, Md.* Previous studies have demonstrated the importance of fluid loss, sodium loss, and potassium toxicity in the mortality from shock. The majority of mice will survive a lethal degree of trauma if 10 to 15 per cent body weight of isotonic sodium solution is administered. However if shocked mice are placed in individual wire cages at a temperature of 18 to 22°C a rapid fall in oxygen consumption and body temperature occurs, with death of the animals within 48 hours. The fall in temperature appears to be secondary to the fall in metabolism.

This phenomenon is largely independent of the fluid and electrolyte disturbance and occurs in spite of adequate saline or plasma therapy. Evidence of toxic factor(s) from the injured tissues is found in that it can be corrected by ligating the traumatized legs after varying intervals of time.

Previous conclusions on the optimum environmental temperature in shock have been based upon survival time of untreated animals. However, in the range of 18 to 31°C an entirely different response may be obtained in treated animals. In tourniquet-shocked mice, adequately treated, the optimum temperature for survival lies between 26 and 29°C, above this range the toxic effects of heat appear.

The physiological disposition of a series of 9-amino acridines. JOHN V. TAGGART (introduced by James A. Shannon), *Research Service, Third Medical Division, Goldwater Memorial Hospital and the Dept of Medicine, New York Univ College of Medicine, New York* (Read by title). The effectiveness of quinacrine when used as an antimalarial is dependent in large measure upon its disposition in the body. This follows from the high correlation between plasma quinacrine concentra-

tion and suppressive antimalarial effect and the extensive localization of quinacrine in various tissues and in parasitized erythrocytes.

The present study is concerned with the relationship between molecular structure and the physiological disposition of a series of 9-amino acridines closely related to quinacrine, but which show a fairly wide range of antimalarial activity in avian and human infections. The series includes compounds with diethylaminoalkylamino and diethylamino-1-methylalkylamino side chains of varying length in the 9 position of 3-chloro-7-methoxy acridine and variations in the nuclear substituents of quinacrine.

Variations in the length and character of the side chain produce marked differences in plasma drug concentrations achieved, in the extent of plasma binding and tissue localization, and in the rate of metabolic degradation. Plasma binding and tissue localization, in relation to the plasma water drug concentration, are greatest when butyl separates the nitrogens of the side chain and are further enhanced by branching of the alkyl group. The chloro nuclear substituent exerts its greatest effect in promoting tissue localization, whereas the methoxyl appears only to increase the rate of degradation.

Variations in antimalarial activity within this series are not related independently to plasma concentration, plasma binding, tissue localization or metabolic degradation, but parallel the cumulative effects of all of these processes involved in disposition. [Based upon work done under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and New York Univ.]

Cinchona Alkaloids. 3. Physiological disposition in man. JOHN V. TAGGART (by invitation), ROBERT W. BERLINER (by invitation), CHARLES G. ZUBROD (by invitation), WILLIAM J. WELCH (by invitation), DAVID P. EARLE, JR. (by invitation) and JAMES A. SHANNON, *Research Service, Third Medical Division, Goldwater Memorial Hospital, and the Dept of Medicine, New York Univ College of Medicine, New York*. A wide range of plasma drug levels is achieved in different individuals receiving the same oral dose of any one of the four alkaloids. On a daily oral dose of 300 mg of quinine, the individual mean plasma drug levels in 30 subjects ranged from 2 to 8.9 mg per liter.

Regimens of quinine administering total daily dose of 0.2, 0.5 or 1.5 grams result in group mean plasma concentrations of 3, 5 or 10 mg per liter. Cinchonine, quinidine and cinchonidine result in plasma concentrations approximating 5%, 25% and 40% respectively of the corresponding quinine levels.

Absorption of all four alkaloids is essentially complete. Peak plasma concentrations are

achieved 1 to 3 hours after an oral dose and are only slightly lower than levels obtained at this time after intravenous administration. The plasma drug level falls rapidly after termination of therapy, only negligible quantities persist beyond 24 hours.

The volume of distribution of quinine 1 hour after intravenous administration is approximately equal to body weight, limited localization occurring in liver and other tissues. Less than 10% of the administered dose is excreted in the urine. Therefore, metabolic degradation must play a dominant rôle among the physiological processes controlling plasma drug concentration. The much lower plasma levels obtained with cinchonine are probably due to a high rate of degradation rather than extensive tissue localization. [Based upon work done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and New York Univ.]

Pamaquin 2 Suppressive antimalarial activity in vivax and falciparum malaria. JOHN V. TAGGART (by invitation), ROBERT W. BERLINER (by invitation), CHARLES G. ZUBROD (by invitation), WILLIAM J. WELCH (by invitation), DAVID P. EARLE, JR. (by invitation) and JAMES A. SHANNON. *Research Service, Third Medical Division, Goldwater Memorial Hospital, and the Dept. of Medicine, New York Univ. College of Medicine, New York.* (Read by title.) A precise definition of the suppressive antimalarial activity of pamaquin was undertaken in blood-induced infections at the same time as its prophylactic and curative activities were examined.

Fourteen patients with blood-induced McCoy vivax malaria received pamaquin in the standard test for suppressive activity. The daily dose varied from 4 to 90 mg of base. Mean plasma drug concentrations ranged from 3 to 570 micrograms per liter. The correlation between oral dosage and effect was poor. Twenty mg of pamaquin produced a maximal effect, and thus only a temporary disappearance of parasitemia and fever.

Similar results were obtained in falciparum malaria. Eight patients with blood-induced McClendon falciparum malaria received pamaquin in the standard test for suppressive activity with this infection. The daily dose was either 30 or 60 mg of the base. Mean plasma concentrations ranged from 36 to 545 micrograms per liter. Class II or partial effects were obtained in all trials.

These observations confirm the conclusion of previous investigators that pamaquin administered to patients with vivax or falciparum malaria has some activity against the erythrocytic forms of the parasites. The activity is not great however, since at maximal tolerated dosage for 4 days in vivax malaria eradication of the erythrocytic

forms of the parasite is not achieved. [Based upon work done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and New York Univ.]

The effect of anesthetics and cerebral vasodilating procedures on the penetration of sulfathiazole into the cerebro-spinal fluid. R. S. TEAGUE and MERVIN PERDUE (by invitation). *Dept. of Physiology and Pharmacology, Medical College of Alabama, Birmingham.* A study has been made of the effect of cerebral vasodilators and vasodilating procedures on the degree of penetration of sulfathiazole into the cerebro spinal fluid. Anesthetized dogs were given 10 cc/kg of a 2.4% sulfathiazole sodium sesquihydrate solution intraduodenally after ligation of the pylorus. Free sulfathiazole levels in the blood and cisternal fluid were determined at hourly intervals thereafter for five hours. The degree of cerebro spinal fluid penetration of sulfathiazole was indicated by the C/B ratios which were obtained by dividing the average of the 3rd, 4th, and 5th hour cerebro spinal fluid sulfathiazole levels by the average of the first four hour blood sulfathiazole levels.

Using animals anesthetized with dial as controls, it was found that the mean C/B ratio under ether anesthesia was 42.5% higher. The mean C/B ratio was not significantly changed under chloroform anesthesia (-11.8%), nor by the administration of CO₂ to animals under dial anesthesia (+11.1%), nor by anoxia (+18.3%), nor after alcohol intravenously (+7.8%). However a significant increase in the C/B ratio was found under dial after rebreathing experiments (+28.8%), after alcohol injected into the common carotids (30.7%), and after saline similarly injected (24.8%). It is concluded that cerebral vasodilatation may be accompanied by increased penetration of sulfathiazole into the cerebro spinal fluid. [Aided by a grant from the Univ. Research Committee.]

Effects of a bone marrow-spleen immune serum on cytology of the spleen. Potentialities as a bioassay method. THURLO B. THOMAS (by invitation), P. L. EWING and G. A. EMERSON. *The Univ. of Texas Medical Branch, Galveston.* Bogomolets' serum (ACS, antitreticular cytotoxic serum) was found to have irregular effects on the leucocyte count and differential picture of blood of individual laboratory animals. Serologic tests such as complement-fixation and precipitin reactions also are unsatisfactory to quantify the purported active principle of ACS. Effects of ACS in tissue culture, as noted by Pomerat et al. (*Texas Repts Biol Med*, 3, 122, 404, 1945), do not fulfil the criteria of good bioassay practice, inasmuch as a "blocking" effect is apparent only in high concentrations at which many normal constituents of

serum may modify the results, and the stimulant effects with 0.25% are not convincing. White mice were injected intraperitoneally with graded doses of an ACS prepared by repeated injection of mouse spleen and bone marrow in rabbits, this serum had a complement-fixation titer of 1:280. Spleen, Peyer's patches, mesenteric lymph nodes, thymus and other tissues were removed at intervals after treatment, sectioned and stained with hematoxylin-eosin. In contrast to the irregular blood responses in these mice, a dramatic, regular change in distribution of small lymphocytes was noted in the spleen with migration from the periphery of the Malpighian corpuscles into the cords of Billroth.

Studies on the fate of tri-p-anisyl chloroethylene and hexestrol. CHARLES R. THOMPSON (by invitation) and HAROLD W. WERNER. *Pharmacology Dept., Research Labs., The Wm. S. Merrell Co., Cincinnati, O.* Tri-p-anisyl chloroethylene has, compared to hexestrol, a low milligram potency and a long duration of action following subcutaneous and oral administration (Fed. Proc. 4:137, 1945).

These differences are partially explained by studies on storage in body fat. Bioassays of fat from castrate female rats, administered three 50 mg doses of hexestrol orally, revealed no estrogenic material. Abdominal fat from rats administered a similar amount of tri-p-anisyl chloroethylene contained approximately 10 mg per cent 1 day later and 2 mg per cent 10 days later. Storage of estrogenic material was not increased by subcutaneous administration of tri-p-anisyl chloroethylene over a three-month period.

Fecal elimination, following three 50 mg doses orally, paralleled fat storage generally. Little or no estrogenic material was found in feces following hexestrol. Activity, greater than 100 per cent of the administered material the first day and about 25 per cent the fifth and tenth days, was found following tri-p-anisyl chloroethylene administration. The high total recovery and spectrographic analyses indicate the fecal estrogenic material was not entirely tri-p-anisyl chloroethylene.

Some recovered estrogen, following oral administration of tri-p-anisyl chloroethylene, may have been unabsorbed material. However, fecal elimination was demonstrated by recovering estrogenic material several days after oral administration and following intraperitoneal administration.

Urinary elimination of estrogenic material following oral administration of both estrogens was very low.

Observations on the central excitatory effects of metrazol. JAMES E. P. TOMAN, LOUIS S. GOODMAN and EWART A. SWINYARD¹ (by invitation). *Depts.*

of Physiology and Pharmacology, Univ. of Utah School of Medicine, Salt Lake City (Read by title). In the visual cortex of unanesthetized rabbits, metrazol produces an episodic slow-wave EEG dysrhythmia when 50 to 75% of the convulsive is injected. With smaller doses the dysrhythmia may be evoked by single cortical shocks. Larger doses produce a spike and dome dysrhythmia in the motor cortex. These dysrhythmias are inhibitable by auditory or painful stimulation. From their rate of disappearance it is calculated that metrazol is inactivated exponentially with an average half-life of 31 minutes. The subconvulsive dysrhythmias and overt seizures due to metrazol are more effectively antagonized by tridione than by the common barbiturates.

Metrazol increases the voltage, frequency, number of waves, and rate of recovery of corticospinal motor discharges evoked by sciatic stimulation in cats under deep barbiturate anesthesia. It increases the voltage of the surface negative component of "spindle" discharges in the EEG of cats and rabbits under light barbiturate sedation, but does not abolish all EEG and neurological signs of barbiturate depression, whereas it quantitatively antagonizes similar effects of tridione.

Although less active on cord than on higher reflexes in cats, metrazol can completely restore multineuronal reflexes depressed by tridione. It is less effective than coramine in antagonizing similar cord effects of benzimidazole.

In contrast to strychnine, metrazol reduces the normal electroshock threshold of rats and synergizes with cellular hydration to produce spontaneous seizures. It does not modify the pattern or duration of maximal electroshock seizures. [Aided by a grant from the Research Fund, Univ. of Utah School of Medicine, Salt Lake City, Utah.]

Studies on myasthenia gravis. Apparent "curare-like" effect of compounds that decrease acetylcholine synthesis. CLARA TORDA and HAROLD G. WOLFF. *New York Hospital and the Depts. of Medicine (Neurology) and Psychiatry, Cornell Univ. Medical College, New York, N. Y.* According to a recently presented concept (C. Torda and H. G. Wolff, *Science*, 98:224, 1943, 100:200, 1944, *J. Clin. Invest.*, 23:649, 1944) the symptomatology of myasthenia gravis is mainly due to the decrease of acetylcholine synthesis. In experiments here presented it was ascertained that the defect in muscle function in myasthenia gravis previously explained (Nevins, S., *Brain*, 57:239, 1934, *J. Neurol. and Psychiatry*, 1:120, 1938, etc.) as being due to the presence of a curare-like agent may be the result of a decrease in the acetylcholine available at the neuro-muscular junction.

"Curare-like effect" in this instance is used to imply that stimulation of the motor nerve after exposure to the given agent is not followed by an

¹Winthrop Research Fellow in Pharmacology

adequate muscle contraction. The sciatic nerve of the frog was stimulated and the contraction of the gastrocnemius muscle registered. The compounds used were injected into the ventricle of the frog. Compounds were selected that decreased acetylcholine synthesis but did not decrease the acetylcholine sensitivity of the muscle. These compounds were found to diminish the amount of contraction that was induced by stimulation of the sciatic nerve. Curare, in low concentrations, also diminished the amount of contraction induced by stimulation of the sciatic nerve. However, it did not reduce the amount of acetylcholine synthesized and, furthermore, it decreased the acetylcholine sensitivity of the muscle.

It may be suggested that apparent "curare like" effect on muscle may be induced by agents that reduce acetylcholine synthesis but do not modify the sensitivity of effector cells.

Chemotherapeutic studies in experimental leishmaniasis. H. B. VAN DIKE and ALFRED GELHORN (by invitation) *Dept. of Pharmacology, College of Physicians and Surgeons, Columbia Univ., New York* (Read by title). The anti-leishmanial activity of 182 compounds was compared with that of a standard drug, Stilbanose, in a routine, 6 day therapeutic course using hamsters infected with *Leishmania donovani*. 137 of the drugs tested were organic compounds and 45 were organo-metallic. About 10 per cent of the LD_{50} was injected intraperitoneally daily for 6 days.

Under the testing conditions none of the 137 organic compounds was active. There was great structural heterogeneity in the group, however, since all were inactive there is no reason to consider structural details here.

Fifteen of the organo-metallic compounds contained one of the following metals: arsenic, bismuth, copper, gold, lead or mercury. In no instance was there any chemotherapeutic effect.

The remaining 30 organo-metallic compounds contained either tervalent or quinquevalent antimony. When tested by the method described, none of the 16 tervalent antimony compounds was active. The prompt therapeutic effectiveness of quinquevalent antimonials, such as Neostibosan, is apparently correlated with the potential formation of stibamic acid from the parent compound. Activity was lost if the free amine group was acetylated or diazotized and coupled. In Stilbanose Sb^{+5} is linked through oxygen to gluconic acid or to diethylamino ethanol. The activity of related compounds was lost if one linkage was directly to carbon or if two were through sulfur. [Work done under contract with the Office of Scientific Research and Development.]

A comparison of the effect of 7% carbon dioxide with 93% oxygen, and pure oxygen, on goats and dogs, acutely asphyxiated with carbon monoxide

K. K. VINING, JR., J. L. WHITTENBERGER, A. C. WOITACK (introduced by P. R. Dumko). *Clinical Research Section, Medical Division, Chemical Warfare Service, Edgewood Arsenal, Md.* A mixture of 7% carbon dioxide and 93% oxygen was used for ten minutes as inhalation therapy on goats and dogs sustaining an arterial saturation of 60 to 80% carbon monoxide. The rate of elimination of carbon monoxide, the effect on blood carbon dioxide levels, on blood pressure and on minute volume of respiration, were compared with similar data on two groups of goats and dogs similarly asphyxiated, but treated with pure oxygen or room air.

The animals treated with 7% carbon dioxide in 93% oxygen eliminated an average of 10% more carbon monoxide than those treated with pure oxygen. The arterial blood pressure fell in all animals and was between 55 and 100 millimeters of mercury in about one third of the animals. The pressure rose to normal in animals treated with the carbon dioxide-oxygen mixture, rose an average of 60% of the acute fall in animals treated with pure oxygen, but continued to fall or remained low in the air treated group.

Minute volume respiration increased an average of 110% when the carbon dioxide-oxygen mixture was breathed. There was no increase when pure oxygen or room air was breathed.

During gassing, the arterial carbon dioxide contents decreased to an average 63% of the original values. In those animals treated with the carbon dioxide-oxygen mixture, the level rose to an average of about 78% of the original values, but remained low or continued to fall in those animals treated with pure oxygen, or room air.

There was no evidence of respiratory or circulatory depression during the period of inhalation of 7% carbon dioxide in 93% oxygen, or following its use.

The interaction between neostigmine and epinephrine and the dimethylpiperidines. A. EARL VIVINO (by invitation) and THEODORE KOPFANYI. *Georgetown Univ., School of Medicine*. Intravenous injections of 2,3 and 2,4 dimethylpiperidine hydrochloride produce a fall of blood pressure which becomes less intense upon each subsequent administration (tachyphylaxis). It usually requires from 25-40 mg per kg of dimethylpiperidine hydrochloride given in divided doses within a period of from 15-30 minutes to bring about autonomic ganglionic depression characterized by annulment of the electrical excitability of the vagus, of the pressor effect of nicotine and of the ocular effects of stimulation of the preganglionic but not the postganglionic portion of the cervical sympathetic. With the onset of the maximum ganglionic effects, doses of neostigmine (0.075 mg per kg by vein) antagonized the ganglionic depression as shown by the almost immediate return

of appreciable cardiac slowing upon peripheral vagus stimulation, restoration of pressor effect of nicotine and ocular effects produced by preganglionic cervical sympathetic stimulation. These effects are comparable to the effect of the neostigmine on the ganglionic depression produced by nicotine or amygdala.

Like sparteine and propylpiperidine, the dimethylpiperidines in paralytic doses also potentiate the pressor effect of epinephrine both in height and duration. This potentiation disappears following the employment of neostigmine.

While nicotine in ganglionic paralytic doses usually produces a state of circulatory collapse, following the injection of paralytic doses of dimethylpiperidines the animals' blood pressure may be maintained at a satisfactory level. When such doses were given to animals in the wakeful state they showed no detectable signs of injury, distress or central depression.

The relation between the chemical structure of DDT and its toxicity with oral administration to mice. W. F. VON OETTINGEN and N. E. SHARPLESS (by invitation) *Industrial Hygiene Research Lab., National Inst. of Health, Bethesda, Md.* DDT (2,2-bis-(p-chlorophenyl)-1,1,1-trichloroethane) and 22 derivatives were studied with regard to their toxicity in mice. It was found that the toxicity and especially the production of tremors depends upon the presence of three chlorine atoms in the ethane group and on substitution of the hydrogen in para position of the phenyl by halogen or by stable ethereal groups of relatively short chain length. The relation between these findings and certain physico-chemical properties of these compounds is discussed and it is shown that the lability of one chlorine atom in the 3-chloroethane group is responsible for the nervous manifestations produced by DDT.

Effects of β -dimethylaminoethyl benzilate HCl on intestinal activity. K. G. WAKIM, CLARENCE E. POWELL (by invitation) and K. K. CHEN *Indiana Univ. Medical Center and Lilly Research Labs., Indianapolis.* A pharmacologic study of the properties of the synthetic antispasmodic, β -dimethylaminoethyl benzilate HCl, revealed that the compound possesses both neurotropic and muscletropic types of antispasmodic action (*J. Lab. & Clin. Med.* 30:700, 1945). The present presentation deals with the effects of the same product on the normal postprandial intestinal activity and on the heightened intestinal activity induced by subcutaneous administration of prostigmine, physostigmine, or pilocarpine, in trained dogs, with a previously prepared skin-covered intestinal loop normally continuous with the rest of the gastrointestinal tract and with circulation and nerve supply intact. After control records were established, the antispasmodic drug was adminis-

tered by various routes, namely, orally, subcutaneously, intramuscularly, or intravenously, and its effects on intestinal activity were recorded kymographically by the use of an air-tight tambour system. β -Dimethylaminoethyl benzilate HCl inhibited both the normal postprandial intestinal activity and the heightened activity induced by prostigmine, physostigmine, or pilocarpine. Under the influence of this drug, the peristaltic and rhythmical segmentation movements were abolished for periods roughly varying with the amount administered. Generally, as the effects of the drug wore off, rhythmical segmentation movements reappeared before peristalsis.

Pamaquine naphthoate, quinacrine hydrochloride, and quinine bisulfate as curative agents in Plasmodium cathemerium infections of the duck. HARRY A. WALKER (by invitation), LESLIE A. STAUBER (by invitation) and ARTHUR P. RICHARDSON *Division of Pharmacology, The Squibb Inst. for Medical Research, New Brunswick, New Jersey.* A standardized procedure has been used in the assay of the curative value of antimalarial drugs against *P. cathemerium* infections in Pekin ducks. The drugs are administered in the diet or by stomach tube for 7 days (one day before and 6 days following inoculation) and the ducks are kept under observation for a total of 30 days. On the 30th day after inoculation a fresh 100 gram duck is subinoculated with blood from each original duck and a positive or negative subinoculation is determined from blood smears made during the observation period of 12-15 days. Following subinoculation each original duck is challenged with a large dose of parasites in an attempt to cause reinfection.

The following criteria of cure are used: (1) the failure to observe any parasites after drug administration is discontinued, (2) the failure to observe parasites in the subinoculated duck, and (3) the ability to produce a normal infection in a duck 30 days after the original inoculation and 23 days after drug therapy. Experiments on the sensitivity of subinoculation as a criterion showed that doses of 50 parasitized cells per kilo or approximately 5 parasitized cells per duck produced consistent infections with varying levels of parasitemia. The marked sensitivity of reinfection became apparent when we were unable to cause reinfection in ducks which received inocula of 10 and 50 parasitized cells per kilo 4 weeks previously and which showed low levels and short periods of parasitemia. The results indicated that a duck is immune to reinfection so long as a primary infection is established irrespective of the parasite density or length of patent period.

To produce a 50 per cent reduction in parasite count with the suppressive procedure in *P. cathemerium* infections, 7 and 14 mg per kg per day of

quinacrine dihydrochloride and pamaquine naphthoate, respectively, were needed. However, approximately 135 and 23 mg per kg per day of these drugs were necessary to produce cures in 50 per cent of the ducks. The fact that the ratios of the curative dose to the suppressive dose for these drugs are approximately the same seems highly significant. Only the relatively high therapeutic index of these drugs in the duck makes these results possible. [The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Squibb Inst for Medical Research.]

Toxicity of methylamino-iso-octene (octin) R P WALTON and C B PREACHER (by invitation) *Dept of Pharmacology, Medical College of South Carolina, Charleston*. Recent observations (Clinics, 4: 552, 1945) that symptomatic relief from migraine headache can be obtained by the use of methylamino iso octene (octin) has attracted special interest to the possibility of toxic effects from its chronic administration. Swiss mice were given octin mucate in approximate daily doses of 40 mgm/kgm in drinking water continuously over a period of 180 days and 2 generations of their progeny received the same medication during this interval. Males of a tumor-susceptible (C_3H) strain of mice received the same medication over a period of 190 days. In the total colony of 175 mice no significant differences between medicated and control groups were noted in appearance, weight curves, fertility and gross autopsies. Young roosters were given single, daily, intramuscular injections of octin hydrochloride in doses of 20 mg/kg for 66 to 132 days, no gangrenous comb changes were noted in contrast to similarly maintained roosters which readily showed typical comb gangrene with ergotamine injections. Ergotamine tartrate in 0.5 mg/kg doses intramuscularly produced acutely much more intense effects on the comb (marked blanching, drooping and cyanosis at tips) than these doses of octin. Three dogs received daily single subcutaneous injections of octin hydrochloride in doses of 4 mg/kg for 167 to 217 days, three dogs received total oral doses of octin mucate of 3.0 to 5.7 grams/kg over periods of 50 to 200 days. Significant cumulative toxic effects of a gross nature were not observed. Tissue specimens from each group of animals are being studied. The acute toxic effects place the main limitation on chronic administration. With dogs, total daily doses of 60 mg/kg orally of the octin mucate given in 2 installments represent the approximate upper limit of tolerance. Larger doses cause intense cocaine like cerebral excitation and weight loss. The LD_{50} of intravenous octin hydrochloride is approximately 30 mg/kg. Doses of 40

mg/kg cause convulsive deaths in 1 to 2 minutes. Open chest observations show the blood pressure fall obtained by excessive or repeated doses is associated with cardiac dilatation.

The treatment of pulmonary edema with suction and certain drugs R A WAUGH and RUTH HORNFR (by invitation). In this work treatment was directed toward the removal and possible prevention of the formation of fluid in the lungs during phosgene poisoning. Thirty-two dogs were given an LD_{50} dose of phosgene and observed continuously day and night. One half of the animals were used as controls. Hemoglobin estimations were made at regular intervals. When pulmonary involvement had developed to a point where the animal was coughing up frothy fluid, and in most cases in a dying state, the trachea was opened, a small catheter inserted and suction applied. Theophylline ethylenediamine, atropine and digoxin were administered when it was felt that they were indicated. The immediate results were often dramatic. Animals which were gasping, deeply cyanosed, and in a condition of shock, in a short time became pink and respiration and reflexes returned to normal. The flow of fluid in some animals was not continuous, but was interrupted by periods of relatively no flow. The amount of fluid removed varied from 100 mls to 450 mls and contained a considerable number of blood cells. Theophylline did not reduce the pulmonary edema. Atropine produced marked respiratory stimulation with increased pulmonary ventilation, but this was not maintained. Digoxin increased the force of the heart. The treatment increased considerably the survival time but had little effect on the survival rate of the animals. Hemoconcentration increased following the gassing and returned to normal as the animal recovered.

One way isonipeaine-barbiturate antagonism E LEONG WAH (introduced by George B Roth) *Dept of Pharmacology and Experimental Therapeutics, The George Washington Univ School of Medicine, Washington, D C*. Methods of preventing convulsions and deaths produced by isonipeaine (demerol or 1-methyl-4-phenylisompeecotic acid ethyl ester hydrochloride) overdosage in mice and rabbits were investigated using as anticonvulsants the sodium salts of barbital, phenobarbital, amytal, pentobarbital, evpal and diphenylhydantoin. Each barbiturate, when administered intravenously in a single dose approximating $\frac{1}{2}$ to $\frac{1}{4}$ its respective LD_{50} , aborted convulsions totally or in part and usually prevented deaths in animals given a lethal subcutaneous dose of isonipeaine (mice, 200 mg/kg, rabbits, 250 mg/kg). The non-barbiturate diphenylhydantoin did not prevent isonipeaine convulsions or increase the percentage of survival.

When the dose of each barbiturate was increased

to about $\frac{1}{2}$ or $\frac{1}{4}$ of its respective LD_{50} for antagonizing isonipeccaine overdosage, it was found that the animals died in respiratory depression, convulsions did not precede death. The time of survival was less than that of the animals which received a lethal dose of isonipeccaine only, and seemed to be directly dependent on the rapidity of action of each barbiturate. Subsequently, it was also found that even when the amount of isonipeccaine was decreased to 25 mg/kg, respiratory failure resulted in animals which had previously received an ordinarily tolerated barbiturate dosage ($\frac{1}{2}$ LD_{50}). Diphenylhydantoin did not act like the barbiturates in this respect.

It is concluded, therefore, that isonipeccaine-barbiturate antagonism acts only in one direction. The barbiturates protect animals from the lethal convulsive effects of isonipeccaine subcutaneously, but isonipeccaine potentiates the depressive properties of the barbiturates.

The effect of cyanide on the electrocardiogram of man JACK WEXLER (by invitation), J L WHITTENBERGER (by invitation) and P R DUMKE *Clinical Research Section, Medical Division, Chemical Warfare Service, Edgewood Arsenal, Md*. Fifteen of sixteen normal subjects who received 0.11 to 0.20 mg NaCN/kg body weight intravenously revealed a sinus pause lasting 88 to 4.20 seconds concomitant with onset of respiratory stimulation. This pause was followed by slow irregular P-waves for several seconds with gradual acceleration of rate beyond control levels. The heart rate generally returned to control levels within three minutes.

In three men executed by inhalation of HCN, there was an initial decrease in heart rate accompanied by sinus irregularity and followed by disappearance of P-waves. These changes were an exaggeration and prolongation of those observed with intravenous injection of NaCN. Nodal rhythm in one and idio-ventricular rhythm in the other two, were present during the auricular arrest. A secondary increase in rate and reappearance of irregular, non-conducted P-waves occurred during the third and fourth minutes. All subjects showed a secondary slowing with A-V dissociation during the fifth minute. Heart rate again increased during the sixth and seventh minutes with return to normal sinus rhythm. Thereafter the heart slowed progressively. Normal A-V conduction in one man and A-V conduction with incomplete A-V block in another, were maintained throughout the execution. The third man developed Wenckebach's phenomenon, 2:1 block and finally complete heart block $3\frac{1}{2}$ minutes after the last breath.

QRS complexes exhibited changes in voltage and form. Two men developed bundle branch block patterns present only during periods of idio-

ventricular rhythm. T-waves showed an early transient increase in amplitude. There was progressive shortening to disappearance of ST segments with T-waves originating high on QRS complexes.

The effect of methemoglobinemia on the respiratory stimulation by cyanide in man J L WHITTENBERGER (by invitation), J WEXLER (by invitation), S HUMPHREY (by invitation) and P R DUMKE *Clinical Research Section, Medical Division, Chemical Warfare Service, Edgewood Arsenal, Md*. Respiratory stimulation by intravenous sodium cyanide was studied in 21 experiments on 16 normal subjects before and after induction of methemoglobinemia by p-aminopropiophenone (PAPP). PAPP was given orally in graded doses producing methemoglobin concentrations of 23-42.7%. Cyanide was given in amounts sufficient to stimulate respiration, usually 0.15 or 0.20 mg/kg. One hour after PAPP the stimulating dose of cyanide was repeated.

Besides standard methods, an instrument was used which recorded photographically velocity of inspired air. Planimetric measurement of the resulting curve permitted determination of volume of each breath. The instrument also facilitated detection of small changes in breathing.

Sodium cyanide 0.11 mg/kg failed to stimulate respiration in 6 of 8 trials, 0.15 mg/kg stimulated in all but 4 of 17 trials, in the remainder 0.20 mg/kg was effective. Circulation time varied from 13.2-28 seconds.

Respiratory minute volume increased to an average rate of 19.7 liters/minute after NaCN 0.15 mg/kg and 23.0 l/m after NaCN 0.20 mg/kg. Volume of individual breaths increased to 1.25-3.92 liters, and hyperpnea lasted 5-13 inspirations (before PAPP).

After methemoglobin production, effects of cyanide were markedly reduced. No significant increase in minute volume occurred, analysis of individual inspirations however revealed slight stimulation in 6 of 21 instances. Often stimulation was evidenced in only one or two breaths, once it lasted longer (9 breaths). In this range, concentration of methemoglobin appeared unrelated to protection against 0.15 or 0.20 mg NaCN/kg.

Reactions of chronic totally decorticated dogs during a cycle of morphine addiction ABRAHAM WIKLER *Research Dept., U S Public Health Service Hospital, Lexington, Ky*. The effects of morphine (1-20 mg per kg) were studied on general behavior, pain threshold (turning of head to opposite side on electrical AC stimulation of tooth pulp through double amalgam fillings), temperature, cardiac rate and respiration in five long-surviving totally decorticated dogs. Three of these preparations were then subjected to regular daily injections or morphine (10-20 mg per kg 2 to 4

times daily) One died on the 10th day of addiction while in 2, addiction was continued for 2 months after which morphine was withdrawn abruptly Another dog was addicted to morphine for 3 months and then decorticated, following which morphine was withdrawn *Single Doses* Morphine regularly caused general sedation, loss of body righting reflexes, lowering of body temperature and cardiac rate and elevation of pain threshold Respirations were variably and only slightly affected *Addiction* Tolerance to elevation of pain threshold by morphine developed rapidly (two weeks) as did also tolerance to general sedative effects, effects on temperature and cardiac rate changed little Later, pre injection temperature and cardiac rate became elevated, motor restlessness and affective irritability (barking and biting when handled) appeared, while pain threshold level remained unchanged *Withdrawal* Following abrupt withdrawal the preparations exhibited marked motor restlessness, elevation of temperature and cardiac rate and rhinorrhea One dog died accidentally In another, the signs of withdrawal subsided after 3 days, and after 1 week morphine again elevated pain threshold and caused general sedation Addiction was resumed in the third preparation and is still maintained The morphine "withdrawal syndrome" was reproduced by injection of eserine (0.5 mg per kg) in a non addicted chronic totally decorticated dog

Effects of a cycle of morphine addiction on conditioned responses and experimental neuroses in dogs ABRAHAM WIKLER *Research Dept., U S Public Health Service Hospital, Lexington, Ky* (Read by title) Conditioned leg withdrawal responses were established in 7 dogs by pairing faradic shocks to one hind leg with pure tones of frequencies from 350 to 500 cycles per second or with a strong light Positive and negative responses were then developed to the limit of the dogs' ability to differentiate between such signals During the first few months of such training morphine (1 to 10 mg per kg) impaired differentiation markedly or abolished the conditioned response altogether In some excitable dogs morphine (0.5 mg per kg) produced mild sedation and improved learning and differentiation In all dogs the effects of morphine were temporarily abolished by nociceptive stimulation As training continued single injections of morphine exerted less effect on conditioned responses and in one dog after 6 months of training morphine ceased to impair differentiation at all Experimental neuroses were produced in 2 dogs by exhibiting negative and positive conditioned stimuli simultaneously One neurosis was characterized by schizophrenic like inhibition and catatonia and the other by manic-like excitement and hyperactivity These two neurotic dogs and one very stable dog which could

not be made neurotic were subjected to daily injections of morphine (10 mg per kg twice daily) for three months Before tolerance appeared morphine reduced the excitability and improved performance in the manic dog, but had little effect on the performance of the other two As tolerance developed all three dogs became increasingly restless and irritable, but this did not impair the differential responses of the stable dog After abrupt withdrawal all dogs showed a mild, but characteristic, "abstinence syndrome" which subsided after 3 to 5 days After this period the behavior and performance of the neurotic dogs remained unchanged while the stable dog became cooperative and friendly and continued to respond correctly to complex conditioned stimuli

The carcinogenic activity of various fluorene derivatives ROBERT H WILSON and FLOYD DRUDS *Pharmacology Division, Bureau of Agricultural and Industrial Chemistry, U S Dept of Agriculture* 2-Acetaminofluorene (AAF) has been shown to be carcinogenic when it is incorporated in the diet and fed to albino rats for a sufficient length of time (Cancer Research, 1:595, 1941) Subcutaneous implantation of AAF powder, or injections of a propylene glycol solution produced minimal changes in some animals after prolonged periods These facts together with some evidence that rats ingesting AAF excreted an amine suggested that 2-aminofluorene was the true carcinogenic agent, deacetylation of AAF having taken place in the gastro intestinal tract When rats and mice were fed diets containing 2-aminofluorene they developed carcinomas resembling those produced by AAF The feeding of 2-chlorofluorene, as an example of a different substituent in the 2 position, did not produce any evidence of malignancy Other compounds which were found to be non carcinogenic were the hydrocarbon, fluorene, its 9 oxidation product fluorenone, and xanthene, a compound which superficially resembles fluorenone In view of the above results, and since beta naphthylamine and 2-aminoanthracene have been reported to have certain carcinogenic properties, it is suggested that an amino group in the 2 position is important in determining carcinogenic activity

The incidence of convulsions in general paretics receiving quinacrine WILLIAM J WELCH, PETER KNOWLTON, FREDERICK S BIGELOW, ELI BAUMAN and ROBERT W BERLINER (introduced by James A Shannon) *Research Service, Third Medical Division, Goldwater Memorial Hospital and the Dept of Medicine, New York Univ College of Medicine, New York* (Read by title) The hazards of quinacrine therapy include toxic effects on the central nervous system Common experience indicates that such phenomena are rare in the treatment of uncomplicated malaria with usual oral doses of

quinacrine This is not the case when quinacrine is administered in therapeutic doses to patients with advanced central nervous system syphilis

In a series of 115 patients with advanced general paresis and extensive organic deterioration who received quinacrine for the termination of therapeutic malaria, 19 convulsive episodes occurred during 1336 patient-days on quinacrine, or 14.2 per 1000 patient-days, as compared with 12 episodes in 10,480 patient-days (1.14 per 1000 patient-days) in the same individuals when not on quinacrine

There were only two convulsions in 1040 patient-days (1.92 per 1000 patient-days) among 153 similar patients who were given quinine, as compared with 17 episodes in 13,033 patient-days (1.31 per 1000 patient-days) in the same individuals when not on quinine

In another group of 150 patients with early neurosyphilis and with less organic deterioration, there were no convulsions during the control observation period and two during 1940 days on quinacrine (1.03 convulsions per 1000 patient-days)

It appears advisable to utilize quinacrine for the termination of therapeutic malaria in patients with advanced organic deterioration due to neurosyphilis [*Based upon work done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and New York Univ*]

Cinchona Alkaloids 6 **Suppressive antimalarial activity of cinchonine carbostyryl** WILLIAM J. WELCH (by invitation), JOHN V. TAGGART (by invitation), ROBERT W. BERLINER (by invitation), CHARLES G. ZUBROD (by invitation), DAVID P. EARLE, JR. (by invitation) and JAMES A. SHANNON *Research Service, Third Medical Division, Goldwater Memorial Hospital, and the Dept of Medicine, New York Univ College of Medicine, New York* The suppressive antimalarial activity of the carbostyryl of cinchonine (first metabolic product) was assayed in the standard blood induced (McCoy) vivax malaria, using 5 subjects, according to the procedure outlined in a preceding abstract A Class III effect, or "cure," was obtained in one test at a mean plasma drug level of 3.4 mg per liter, Class II or partial effects in two tests at 2.4 and 1.3 mg per liter and Class I or no effect in two tests at 1.1 and 0.7 mg per liter A daily oral dose of 3 grams was required to achieve the Class III effect Daily oral doses and mean plasma drug levels of 1 gram and not more than 0.1 mg per liter, respectively, are required to achieve Class III effects with the parent drug cinchonine The inherent suppressive activity of the first metabolic product of cinchonine is, therefore, much less than that of cinchonine itself Since, dose for dose, the same plasma cinchonine

carbostyryl level is achieved whether cinchonine or its carbostyryl is administered, it appears that the carbostyryl contributes little to the antimalarial effect which is produced when cinchonine is administered Further, Class III effects, or "cures," are achieved at extremely low plasma cinchonine levels, as compared with those of the other 3 cinchona alkaloids These findings raise the question of whether cinchonine itself is, in fact, the active agent, or, perhaps, whether the antimalarial action of cinchonine is related to its potentiality to undergo oxidation to a carbostyryl [*Based upon work done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and New York Univ*]

Pantoyltauramides as antibacterial chemotherapeutic agents H. J. WHITE, M. E. LEE, E. R. JACKSON, A. T. HIMS and C. ALVERSON (introduced by J. T. Litchfield, Jr) *Chemotherapy Division, Stamford Research Labs, American Cyanamid Company* Several new analogues of pantothenic acid have been compared quantitatively with reference to their antibacterial activity in vitro, activity in infections in mice, mechanism of action and their absorption, excretion and acute toxicity in mice and rats Included in this study were pantoyltauramido-benzene, naphthalene, pyridine, pyrimidine and quinoline derivatives The following conclusions appear to be justified

In vitro, many of the compounds are highly active against strains of *Streptococcus hemolyticus*, Groups A and B, and *Streptococcus viridans* Anti-streptococcal indexes of 25 to 50 were obtained for eleven analogues, all of which were equally active against sulfadiazine-susceptible and sulfadiazine-resistant strains Against strains of several other pathogenic species, most of the analogues are practically inactive

In contrast to pantoyltaurine, many of these analogues are highly active in a hemolytic streptococcus infection in mice Median Survival Doses for eleven analogues ranged from 4 to 12 milligrams per 20 gram mouse, administered as a single oral dose The antibacterial activity of most of the analogues is reversed by added pantothenate, both in vivo and in vitro

When administered orally, the therapeutic activity of certain analogues, as well as the inactivity of others, correlates with their absorption, as indicated by peak and duration of blood concentration-time curves The compounds appear to be relatively non-toxic to mice and rats

In contrast to other highly active analogues, only limited amounts of d-(+)-pantoyltauramido-4-chlorobenzene and d-(+)-pantoyltauramido-3,5-dibromobenzene can be reversed by pantothenate

Antidotal action of metrazol against pentothal sodium overdose R W WHITLEY and L W ROTH (by invitation), and W B DRAFFER *Dept of Physiology and Pharmacology, Univ of Colorado, Denver* In the present series of experiments an attempt has been made to determine the analeptic effect of metrazol against pentothal sodium overdose Controls were established in 20 dogs by determining individually for each dog the (M)inimal (D)ose of pentothal sodium required to produce (R)espiratory (A)rrrest or M D R A in at least two of three administrations In a second series 10 mg/kg of metrazol was given intravenously one minute before completion of the injection of pentothal sodium Resuscitation was conducted by manual artificial respiration and oxygen Results (1) The M D R A of pentothal sodium ranged from 26.15 to 52.56 mg/kg (median = 34.38) (2) The incidence of respiratory arrest following 71 control administrations of the M D R A was 57 or 80.3% Following 63 administrations of the M D R A plus metrazol the incidence of respiratory arrest was only 30 or 47.6% (3) There were 3 or 2.2% failures to resuscitate from 137 control respiratory arrests but when metrazol was administered there were 2 or 6.7% failures to resuscitate from 30 respiratory arrests Metrazol, therefore, antidoted the respiratory depressant action of an overdose of pentothal sodium with moderate success but did not diminish the probability of death (4) Metrazol had no significant effect upon the length of time the animals slept after pentothal sodium or upon the length of time required to resuscitate from respiratory arrest

Accumulation of DDT in the fat of rats in relation to dietary level and length of feeding GEOFFREY WOODARD and RUTH R OFNER (introduced by Bert J Vos, Jr) *Division of Pharmacology, Food and Drug Administration, Federal Security Agency, Washington, D C* Following the observation that orally administered DDT tends to accumulate in the adipose tissues of dogs (Woodard, Ofner and Montgomery, *Science* 102: 177-178, Aug 17, 1945), an investigation of a similar phenomenon in rats was made to determine in what way accumulation is dependent upon rate and length of DDT feeding Adult white rats were fed 50, 100, 200 and 400 p.p.m. of DDT in their ration for periods from 18 to 90 days These animals were sacrificed and the amount of DDT in the fat was determined by the Schechter-Haller colorimetric method Accumulation was found to increase with dietary level and with length of administration up to 54 days Beyond this time the concentration in the fat tended to remain the same on all levels but the highest Females were found to have higher fat concentrations of DDT than males fed under the same conditions In an additional experiment female rats fed diets containing 12.5 and 25 p.p.m. DDT providing

average daily intakes of 0.85 and 1.65 mg/kg for 51 days showed appreciable storage in the fat (150 and 300 p.p.m.) (A portion of the funds used in this investigation was supplied by a transfer, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Division of Pharmacology of the Food and Drug Administration)

Electro-uterography and the physiology of the human uterus as related to dysmenorrhea and metrorrhagia R A WOODBURY, GEORGE P CHILD (by invitation), RICHARD TORIN (by invitation), WALTER G WATSON (by invitation) and LOUISE JARNOZ (by invitation) *Depts of Pharmacology and Obstetrics and Gynecology, Univ of Georgia School of Medicine, Augusta* Patients were available at various times of the menstrual cycle Uterine and cervical pressures were recorded simultaneously with an optical system from balloons inserted in the uterus and cervical canal On the same paper an electrocardiograph was adapted to record simultaneously the action currents picked up through silver chloride coated silver electrodes Records taken from the same patient before and after hysterectomy showed that extra-uterine visceral action currents seriously interfered with interpretation of any records taken with electrodes outside the reproductive tract

Impulses appear to originate normally in the upper portion of the fundus of the uterus and in the cervix However, in dysmenorrhea patients multiple origin of impulses frequently occurs and contractions are superimposed upon each other They may remain as organized contractions and develop high pressures or become disorganized and develop various forms of uterine tetany

In control patients, between contractions the uterine and cervical pressures in mm Hg were 30 and 20, and during contractions the pressures reached 100 and 40 In uterine dysmenorrhea patients the tone was elevated sometimes so high that pressures of 100 in the uterus and 90 in the cervix were present between contractions, and pressures as high as 300 and 120 were recorded during contractions In labor the highest recorded pressure developed by the human uterus is 100 mm Hg Uterine pulsations of arterial origin disappear at pressures above the arterial blood pressure, which proves that blood flow to the uterus is interrupted at these high pressures

Typical dysmenorrhea symptoms and tracings could not be elicited in any patient by intravenous administration of acetylcholine, histamine or pitocin, but could always be elicited by pitressin and/or by distention of the uterus These data suggest possible methods for scanning compounds for possible uterine antispasmodic activity (see these abstracts, Huggins et al) [Financial grants

Eli Lilly and Company and from Frederick Stearns and Company supported these studies]

Cholinergic action of the anti-sympathetic agent priscol (benzylimidazoline HCl) FREDRICK F YONKMAN, HARRY W HAYS (by invitation), ANNE CAMERON (by invitation), ELIZABETH PELLITT (by invitation), NICOLINE HANSEN (by invitation) *Dept of Pharmacology, Research Division, Ciba Pharmaceutical Products, Inc, Summit, N J* (Read by title) The ileum (Thiry-Vella Loop) of dogs was markedly stimulated by Priscol hydrochloride, 0.5 to 2 mgm per kg, administered intravenously. This stimulation was completely prevented or corrected by atropine sulphate, 0.1 to 0.2 mg per kg whether administered intravenously, intraperitoneally or intramuscularly. Trasentine hydrochloride, 1.0 to 4 mg per kg, administered by the same routes as atropine, also antagonized the stimulating action of priscol. Since trasentine and atropine possess anti-cholinergic properties it is reasonable to conclude that priscol behaved cholinergically in these experiments, especially since they defeated priscol's stimulation of intestinal motility.

If this cholinergic action were to prevail generally, favorable clinical results, as reported following the treatment of Raynaud's Disease with priscol, could probably be due as much to cholinergic fasciculation as to the anti-sympathetic action of the drug. Contemplated experiments should confirm or negate the concept that this drug may exert significant cholinergic actions while simultaneously blocking sympathetic functions.

Adrenergic potentiation by pyribenzamine HCl (N'-pyridyl - N'-benzyl - N' - dimethylethylenediamine HCl) FREDRICK F YONKMAN, DOROTHY CHESSE (by invitation), HARRY W HAYS (by invitation), BARBARA RENNICK (by invitation) and RUDOLF MAYER (by invitation) *Depts of Pharmacology and Bacteriology, Research Division, Ciba Pharmaceutical Products, Inc, Summit, N J*
Counteracts histamine-induced

"Asthma" in guinea pigs

Contraction of intestine and bronchi of guinea pig

Contraction of bronchi in the dog

Hypotension in the dog

Contraction of intact dog intestine

Salivation in the cat

Wheal formation in the rabbit

Counteracts anaphylactic

Shock in the guinea pig

Constriction of bronchi in perfused lung of guinea pig

Hypotension in the dog

Constriction of the intestine in the dog

Other actions include those of analepsia and local anesthesia. Another very important characteristic of pyribenzamine is its capacity for poten-

tiating adrenergic functions. The action of epinephrine has been potentiated in promoting salivation and retraction of the nictitating membrane in the cat, in inhibiting the dog intestine, and occasionally in elevating arterial tension more than normally in experimental animals. Although pyribenzamine intravenously resulted in variable degrees of hypotension in normal animals, it frequently produced hypertension in dogs sensitized to horse serum. This could be interpreted as resulting from adrenergic potentiation by the anti-allergic agent.

If adrenergic potentiation likewise prevailed in the clinical patient it might be an important method whereby clinical relief might be obtained, since epinephrine (or sympathin) frequently produces such marked benefits in certain allergies.

This potentiality has been studied by Dr Koepf and his co-workers in Buffalo and their results are reported elsewhere in this journal.

It is conceivable that pyribenzamine might elicit such adrenergic potentiation by interfering with some enzymic system such as amine oxidase or tyrosinase. This hypothesis warrants investigation.

Cinchona Alkaloids 2 Comparative suppressive antimalarial activity CHARLES G ZUBROD (by invitation), ROBERT W BERLINER (by invitation), JOHN V TAGGART (by invitation), WILLIAM J WELCH (by invitation), DAVID P EARLE, JR (by invitation) and JAMES A SHANNON *Research Service, Third Medical Division, Goldwater Memorial Hospital, and the Dept of Medicine, New York Univ College of Medicine, New York*. The suppressive antimalarial activity of the four cinchona alkaloids has been appraised in a standard fashion, using blood-induced (McCoy) vivax malaria.

Class III effects or "cures" are obtained with quinine at plasma drug concentrations of 5.0 mg per liter, cinchonidine at 2.0 mg per liter, quinidine at 0.9 mg per liter, and cinchonine at less than 0.1 mg per liter. Cinchonine exerts a striking antimalarial effect at plasma drug concentration of a different order from that required for the remaining alkaloids.

The erythrocytic phase of the sporozoite induced McCoy strain vivax malaria has been shown to have the same susceptibility to quinine as that of the blood-induced disease, a fact of importance. However, the erythrocytic forms of another vivax strain (Chesson), originating in the Southwest Pacific, as well as those of both Costa and McClenodon strains of falciparum malaria, are considerably more resistant to the suppressive action of quinine and the other cinchona alkaloids.

When the effectiveness of the cinchona alkaloids is defined in terms of oral dosage, the antimalarial activities are found to be approximately the same, with the exception of quinidine, which is somewhat

more active. Since the effective plasma drug levels of the alkaloids are so different, a study of the physiological disposition of these agents was of interest [Based upon work done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and New York Univ.]

Pamaquin 4 Occurrence of leucopenia CHARLES G. ZUNNOR (by invitation), PETER KRONITON (by invitation), WILLIAM J. WELCH (by invitation), ROBERT W. BERLINER (by invitation), JOHN V. TAGGART (by invitation), DAVID P. EARLE, JR. (by invitation) and JAMES A. SHANNON. *Research Service, Third Medical Division, Goldwater Memorial Hospital, and the Dept. of Medicine, New York Univ. College of Medicine, New York* (Read by title). The occurrence of a marked granulocytopenia has been a sufficiently consistent finding in patients receiving pamaquin at high dosage for it to be considered a manifestation of drug toxicity.

Pamaquin in daily doses of 90 mg. (base) when given for 14 days to patients with vivax malaria, alone or in combination with quinine, resulted first in a rise and then in a fall in polymorphonuclear neutrophil (PMN) count. The mean control count

in a group of 12 patients was 5195 per cu. mm. The mean minimum count, usually noted at the end of therapy, was 1870, representing a mean fall in PMN count of 3325 per cu. mm. The mean fall in PMN in a group of 11 patients treated with 30 mg. pamaquin daily was 1750 per cu. mm. as compared with 1270 for the control group whose malaria was treated with quinine alone. The effect on the PMN count of the combination of quinine and pamaquin was no different from that of pamaquin alone. However, the depression of PMN count by the combination of quinacrine with pamaquin at daily dose of 30 mg. was as great as that resulting from daily doses of 90 mg. of pamaquin alone.

The polymorphonuclear neutrophils are the only white blood cells affected by pamaquin therapy. The remaining PMN's show a younger distribution than normal, but no morphological changes. The PMN count gradually returns to normal on stopping the drug. No increase in PMN count was noted in the two instances where pyridoxine was tried in an attempt to reverse the process [Based upon work done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and New York Univ.]

THE AMERICAN SOCIETY FOR EXPERIMENTAL PATHOLOGY

THIRTY-FIRST ANNUAL MEETING

Atlantic City, N. J., March 11, 12, 13, 14, 15, 1946

(For possible corrections in any of the following abstracts see the next issue)

Effect of a bacterial polysaccharide and of tourniquet shock on peripheral capillary circulation in unanesthetized mice GLENN H. ALGIRE. *National Cancer Inst., National Inst. of Health, United States Public Health Service*. Microscopic studies by *in vivo* methods were made of the effects of a bacterial polysaccharide from *B. prodigiosus* and of tourniquet shock on the peripheral capillary circulation in unanesthetized mice. Photographs and daily quantitative measurements were made of the vascular supply in tissue included within a transparent chamber introduced into a dorsal skin flap in the mouse.

In the development of both tourniquet shock and the reaction to the intraperitoneal injection of bacterial polysaccharide, there occurred a decrease in the capillary supply to the panniculus carnosus layer of striated muscle. This quantitative decrease in capillary circulation was ac-

companied by stasis, rouleaux formation, and occlusion. Capillary dilatation was not observed.

After the injection of bacterial polysaccharide, evidence was obtained suggesting an increase in capillary permeability as manifested by edema of the subcutaneous tissues in the chamber. On the other hand, release of tourniquets applied to the hind legs resulted in edema localized in the injured area, without evidence of increase in capillary permeability in the peripheral tissues.

The reactions of tourniquet shock and of injection of bacterial polysaccharide were similar in that both resulted in decreased capillary circulation in the chamber area. They were dissimilar, however, in that edema was apparent after injection of bacterial polysaccharide, but not during the development of tourniquet shock. These experiments do not support the concept of a systemic increase in capillary permeability in tourniquet shock.

Spinal fluid protein in the retrospective diagnosis of sub-clinical poliomyelitis M B ANDILMAN (by invitation), WILLIAM I FISHBEIN (by invitation), and ALBERT E CASRY *Labys of the Chicago Health Dept and the Birmingham Baptist Hospitals* Spinal fluid protein determinations were made 10-60 days after the onset of fever in 31 children suspected of having sub clinical poliomyelitis Eleven of 13 children (85%) had protein levels above 45 mg 10-35 days after onset, averaging 58.2 The cell count was often under 5 Fifteen of 18 (85%) had protein levels under 45 mg 35-60 days after onset, averaging 33.0 The trend of the protein curve was similar in both clinical and sub-clinical poliomyelitis The peak was 7-21 days after onset of fever but abnormally high levels were generally present as late as 35 days

Each child had been an intimate contact (5-21 days prior to the onset of fever) with a patient in the infectious period of poliomyelitis and no other infectious disease (except coryza) recognized in the neighborhoods at the time Daily temperatures were recorded and stools, nose and throat specimens were collected for animal inoculation on most of the 31 children Approximately half had asymptomatic fevers ranging between 98.8° and 99.8° axillary and none had a cough, only one a running nose, and only two a mild diarrhea

The spinal fluid protein averaged 33.0 mg in 38 control children during the same period Two were contacts convalescing from coryza Seven were non-contacts in the patients' neighborhood, and 29 children in control neighborhoods having pertussis, pneumonia, bronchitis, earache, arthritis, measles, scarlatina, diarrhea, abscess, or coryza Only 2 levels were abnormal (46, 49 mg)

The spinal fluid protein level 1-5 weeks after onset in febrile contacts of poliomyelitis patients seems an important and inexpensive adjunct in the recognition of sub-clinical poliomyelitis, a category now containing most poliomyelitis patients

Dietary influence on phospholipid turnover in liver and plasma JESSE L BOLLMAN and EUNICE V FLOCK (by invitation) *Division of Experimental Medicine, The Mayo Foundation, Rochester, Minn* The rate of phospholipid formation was determined after the administration of P³² as sodium phosphate to rats which had been receiving specific diets for two or more weeks previously Rats fed a commercial stock diet were compared to fasting rats and rats that were receiving isocaloric values of diets containing a salt mixture 2 and vitamin supplements including 4 mg choline daily and I, casein 47, crisco 13, sucrose 38, II, casein 6, crisco 13, sucrose 79, III, casein 6, crisco 43, sucrose 49, IV, casein 47, crisco 43, sucrose 8, and the same 4 purified diets from which choline was omitted The relative size of the liver varied

with the diets as did the concentration of phospholipid and its rate of turnover in the liver When calculated in terms of whole liver or body weight there was no significant difference in the rate of phospholipid formation in the liver or its transfer to the plasma, except for a small reduction in rate of phospholipid formation in the rats receiving the choline free diets II and III (protein deficient) The administration of choline caused an immediate increase in phospholipid formation only in those rats that had been receiving the choline free diets II and III

The amount and rate of turnover of phospholipid in the liver is not materially changed by large alterations in the protein, fat or carbohydrate content of the diet In the absence of sufficient protein in the diet, phospholipid formation in the liver is influenced by choline

The influence of the essential amino acids upon appetite in protein-depleted adult white rats PAUL R CANNON, ROBERT W WISSLER (by invitation), C HAROLD STEFFER, JR (by invitation), ROBERT L STRALBE (by invitation) and LAURENCE E FRAZIER (by invitation) *Dept of Pathology, The Univ of Chicago* Two types of rations, one containing sixteen crystalline amino acids in a mixture patterned after the amino acid composition of casein, and the other identical except for the absence of one essential amino acid, were fed to protein-depleted adult white male rats in order to determine the influence of individual essential amino acids upon the ability of the animals to recover lost weight The rats ate the "complete" ration well and recovered lost weight about as quickly as if they had been fed casein at a corresponding nitrogen concentration On the other hand, when any one of the nine essential amino acids, viz, tryptophan, histidine, phenylalanine, leucine, isoleucine, valine, threonine, methionine and lysine, was omitted from the ration, the animals continued to lose weight Concomitantly there was an abrupt decline in food-consumption In contrast, the readdition to the ration of any one of these essential amino acids was followed just as quickly by enhanced food-consumption and rapid weight recovery Neither type of effect was manifested by arginine The significance of these findings will be discussed in relationship to the problem of evaluation of the nutritive properties of protein foodstuffs as influenced by their amino acid composition

Experimental studies on the mechanism of the formation of intraperitoneal adhesions JACOB CHANDY and JONATHAN E RHOADS (introduced by I S Ravdin) *Harrison Dept of Surgical Research, Schools of Medicine, Univ of Pennsylvania, Philadelphia* The formation of adhesions in Wistar rats was standardized (1) by chemical means and (2) by trauma, crushing the wall of the

cecum with a hemostat. One hundred per cent of the animals formed adhesions by each method. A total of 650 rats was used for all experiments.

Mechanical removal of serosa alone did not produce adhesions. Mild chemical injury presumably affecting only the serosa did not produce adhesions. Large amounts of serous exudate were often found in both experiments.

The speed at which the adhesions were formed depended on the depth of the trauma to the intestinal wall.

Heparin in the peritoneal cavity did not influence the formation of adhesions.

One hundred per cent of the animals formed adhesions after the introduction of talcum powder in doses as small as 50 mg. into the peritoneal cavity. No observable amount of serous exudate was found under these conditions.

When the animals were starved seven days adhesions were not formed as rapidly nor as abundantly.

The intraperitoneal injection of 20.0 ml. of physiological saline solution within one half hour following the injury increased the rapidity with which the adhesions were formed.

Introduction of hyaluronidase into the peritoneal cavity prevented the formation of adhesions in 60 per cent of a series of 20 animals.

The data indicate that the blood coagulation mechanism is not necessary for adhesion formation and that the process cannot be stopped by heparin in doses that would readily prevent coagulation. The effect of hyaluronidase was statistically significant and suggests the possibility that hyaluronic acid or some related substance may play a rôle in the formation of adhesions.

The existence of variations in the ease with which thrombin preparations may be inactivated by antithrombin. J. R. CARTER (by invitation) and H. P. SMITH, *Depts. of Pathology, State Univ. of Iowa and Columbia Univ.* The inactivation of thrombin by antithrombin is influenced by a rather large number of variables (eg., temperature, pH, electrolytes, thrombin, heparin, heparin co-factor). Heparin probably acts as a catalyst. By keeping time, temperature, pH, and electrolyte concentrations constant, it has been possible to demonstrate an empirical relationship between co-factor and thrombin destruction.

$$\log \frac{Y}{P} = K + N \log \frac{X}{P},$$

where Y represents the number of thrombin units destroyed in each cubic centimeter, X is the number of units remaining, and P is the relative amount of co-factor, K and N are constants.

Additional study showed that the values of K and N were not constant under all conditions,

indicating the existence of one or more variables previously unrecognized. Thus, thrombin prepared in the dry state for clinical use was not as readily inactivated as preparations freshly prepared and promptly studied. This "resistance" of certain preparations was more notable when small amounts of thrombin were employed. Special treatment of thrombin with heat or with acids can render them partially "resistant" to antithrombin. It is suggested that this alteration may represent changes in colloidal properties, or a special type of denaturation of the thrombin molecule. It is conceivable that physiological variations in ease of inactivation may occur in the thrombin produced in the living body. Evidence indicates that thrombin formed *in vivo* is far more "susceptible" to inactivation than any of the purified preparations thus far studied.

Changes in the thyroid and other organs in mice receiving thiouracil. ALBERT J. DALTON, HAROLD P. MORRIS (by invitation), and CELIA DUNNICK (by invitation). *National Cancer Inst., National Inst. of Health, United States Public Health Service, Bethesda, Md.* Fifty C3H female mice were placed on a diet composed of natural foodstuffs and containing 0.375% thiouracil. Except for a few mice killed at earlier intervals, the mice were maintained on this diet for 26 weeks at which time the thiouracil content was raised to 0.5%.

Of 14 mice killed or found dead after 11 months or more on thiouracil, unencapsulated pulmonary metastases of thyroid tissue were identified in 5. In two of these, thyroid tissue was found in the neck muscles outside the gland capsule. In one other animal of the 14, thyroid tissue was identified between the epithelium of the trachea and the trachealis muscle. All the thyroid tissue found in abnormal sites was present in the form of hyperplastic thyroid follicles consisting usually of a single layer of tall polyhedral cells with large vesicular nuclei surrounding small lumens which occasionally contained pale staining acidophilic colloid.

Gross and microscopic changes in the thyroid, adrenals, ovaries, and uterus were in general similar to those noted and previously reported for thiourea (H. Nat. Cancer Inst. 5:451, 1945). Changes not reported for thiourea include an increase in iron-containing pigment in the spleen and liver. Iron-positive pigment was noted in vacuoles present in proximal tubule cells of the kidney and in some cells lining the thyroid follicles. Pigment negative for iron was seen in the epithelial cells of the bronchi and bronchioles. Stones variable in number and size consisting of a granular, greenish-yellow material were found frequently in the urinary bladder.

Studies on the rate and completeness with which intravenously injected radioactive iron

is utilized REUBENIA DUBACH (by invitation), CARL V MOORE and VIRGINIA MINNICH (by invitation) In the tracer or radioactive iron method for studying absorption of iron from the gastrointestinal tract, measurement is made of the amount of the isotope which appears in red blood cells as newly synthesized hemoglobin The assumption is made that all of the iron retained by the body is utilized for hemoglobin formation The studies here reported were made to test the validity of this assumption

Radioactive iron was given intravenously as ferrous ascorbate in doses of 10 to 25 mg of iron to normal subjects and to patients with various types of anemia In individuals with hypochromic anemia, 100% of the injected radio iron appeared in the peripheral blood by the ninth day In normal subjects the rate of utilization was slower 70% was present by the tenth day but 100% was not found until about ten weeks after injection Patients with hypoplastic or refractory anemia utilized only 1 to 1.5% of the dose for hemoglobin synthesis When administration was made to subjects with pernicious anemia in relapse 27 to 33% of the injected isotope appeared within nine days The values tended to stabilize at this level until liver therapy was begun As the red cells and hemoglobin then rose, the amount of radioactive iron in the blood stream increased until 100% was present In patients with various types of hemolytic anemia 14 to 66% of the isotope appeared in the circulating hemoglobin within 6 to 9 days Usually there was no further increase

These results suggest that in patients with refractory anemias, hemolytic anemias, and pernicious anemia in relapse, the amount of iron absorbed from an oral dose cannot be measured by determining the amount of radioiron which appears in the circulating blood

Hyalinization of glomeruli produced in strain A mice by the administration of urethane (ethyl carbanate) THELMA B DUNN AND C DONALD LARSEN (by invitation) *National Cancer Inst., Bethesda, Md* When weekly doses of urethane were given to strain A mice, it was observed that after a period of 10 to 13 weeks, many of the animals developed severe anasarca At autopsy the kidneys were brownish in color, the size appeared slightly reduced, and the surfaces were smooth Microscopically the kidney had some resemblance to chronic glomerulonephritis in man Most of the glomeruli showed extreme hyaline degeneration with frequent adhesions to Bowman's capsule Dilatation of the tubules, and many granular and hyaline casts were present When the kidneys were examined at earlier periods, progressive stages in the development of the glomerular lesion could be recognized Inflammatory reactions apparently played no part in its development, but dilatation of the glomerular capillaries and ap-

parent fusion of glomerular loops with hyaline formation was an important early reaction

Glomerular lesions of this type were produced only in strain A mice Other strains of mice, C, C3H, and I, and rabbits have so far failed to develop this unusual response under similar experimental conditions

This glomerular lesion in strain A mice is considered of interest because (1) At this period in our investigation it appears to be restricted to one inbred strain in one species of animal, and therefore illustrates how definitely genetic constitution may modify response to a particular agent (2) A glomerular lesion has been produced in which a vascular condition, without inflammatory reaction appears to be the important element in pathogenesis

The cellular sources of antibodies and other globulins W E LURICH, T N HARRIS (by invitation) AND E MERTENS (by invitation) *Philadelphia General Hospital, The Children's Hospital of Philadelphia, and the Depts of Pathology and Pediatrics, The School of Medicine, Univ of Pennsylvania* Though the lymphocytic theory of antibody formation has now been established, it has not been ruled out that other inflammatory cells such as the macrophages or plasma cells are also instrumental in antibody synthesis In order to investigate this question, we first compared the relative antibody titers in the foot pad, the popliteal lymph node, and the blood serum of rabbits that had been injected subcutaneously with dysentery vaccine with or without paraffin oil, we then studied the relative antibody titers in the peritoneal fluid and the peritoneal cell extract of rabbits injected intraperitoneally with various dysentery and typhoid antigen combinations As in spite of excellent antibody response, the granulocytic infiltrations and mononuclear granulomata in the foot pads, as the supernatant fluid of the peritoneal exudate, showed only insignificant quantities of agglutinin, while the isolated granulocytes and macrophages of the exudate revealed no agglutinin at all, and similar results were obtained by intravenous injection of antibody and subsequent intraperitoneal introduction of an irritant, it was concluded that the granulocytes and macrophages do not synthesize agglutinin, the low antibody titer at the site of injection being due to fixation in the sense of Menkin As to the plasma cells, we have found no evidence thus far to show that they produce gamma globulin, it seems possible, however, that they produce beta globulin or related proteins

The pathology of experimental frostbite NATHAN B FRIEDMAN AND KURT LANGE (by invitation) *The Army Institute of Pathology, Washington, D C The New York Medical College, Flower and Fifth Avenue Hospitals, and the Metropolitan Hospital Research Unit* The pathologic

changes in the tissues of rabbits subjected to severe cold are reported. Exposure of the animals' legs to a subfreezing temperature (-30°C) caused gangrene within a week. Agglutinative erythrocytic thrombi picked the engorged vessels, and columns of red cells penetrated the vascular walls and adventitia even in the absence of local hemorrhage. Some vascular channels contained central or parietal hyaline masses. The agglutinated red cells fused and hemolyzed. Rarely, necrotizing angitis was encountered. There were generalized edema, cellular infiltration and vesiculation of the skin. Necrosis involved the deep tissues, including muscle, as well as the skin and subcutaneous structures, and zones of cellulitis bordered the regions of gangrene. No intrinsic neural degeneration could be demonstrated, but damage to myelin sheaths and, in lesser degree, to axis cylinders was evident in diffusely necrotic tissue.

Exposure of the legs of heparinized animals to cold resulted in a few small vesiculating necrotizing lesions of the skin and superficial tissues, but gangrene and necrosis of deep structures did not occur. Edema and proliferation of fixed tissue elements were more evident than in sections from nonheparinized rabbits. Neural degeneration was not noted. There were scattered hemorrhages, but the vessels appeared unchanged and abnormal configurations of red cells were not encountered.

The observations support the view that the fundamental lesions in frostbite involve the vessels.

Osteo-sarcoma from intravenous beryllium compounds in rabbits. LEROY U GARDNER and H F HESLINGTON (by invitation), *The Saranac Laby for the Study of Tuberculosis, Saranac Lake, N Y*. In seeking the cause of an unusual incidence of pulmonary sarcoid in a group of apparently unrelated industries the toxicology of eighteen different chemicals was assayed by routine methods in rabbits, guinea pigs, white mice and rats. Among them were a pure, synthetic zinc beryllium silicate, its ingredients, beryllium oxide, zinc oxide and silicic acid and zinc silicate.

Both beryllium compounds produced results never encountered during the injection of sixty-five different minerals into the ear veins of rabbits (20 doses totaling 1 gram of particles, 3 microns and under, over a six week period). The same effects were not produced by other methods of administration in rabbits nor by any method in guinea pigs and rats. Mice not done.

The rabbit's spleen promptly atrophies, its liver develops progressive cirrhosis and the long bones, spine and ribs undergo progressive cortical sclerosis with ultimate replacement of most of the marrow cavity by hard osseous tissue. Among seven rabbits surviving injection of zinc beryllium silicate for seven or more months all developed malignant osteo sarcomas, often with multiple

primary sites, one died of tumor at $5\frac{1}{2}$ months. One other killed a year after injecting beryllium oxide had a similar tumor. Visceral metastases developed in four.

These compounds contain no fluorine, the silicate fluoresces in ultra violet, X radiation, etc., but affected bones give no evidence of radiant energy by Geiger counter. They are soluble and beryllium cannot be detected by spectroscopic examination four months after injection. Zinc oxide, zinc silicate and silicic acid have no such action. No malignancy has been observed in human beings although their bones have been X-rayed for sarcoid lesions. Beryllium compounds have not produced sarcoid in animals.

The effect of BAL therapy on the renal lesion in mercury poisoning. ARTHUR M GINZLER (introduced by Arnold R Rich), *Pathology Section, Medical Division, Chemical Warfare Service, Edgewood Arsenal, Md*. The therapeutic effectiveness of BAL (2,3-dimercaptopropanol) in lewisite and other arsenical intoxication has been abundantly shown (Science 102: 601, 1945). In association with Gilman's studies (personal communication) demonstrating further its marked value in mercury poisoning, a study has been made of the effect of BAL therapy on the anatomical lesions caused by mercury.

Intravenous administration to rabbits of 3 mg / kg of mercuric chloride, an amount lethal in about 2 to 5 days, results in very extensive to complete necrosis of the renal proximal convoluted tubules, and glomerular damage, evidenced by plasma leakage, and, occasionally, focal glomerular necrosis. In striking contrast, BAL therapy beginning 5 minutes later with the dose (0.15-0.30 mM / kg) optimal in reducing mortality (Gilman, personal communication) results in complete prevention of the necrotizing action of mercury and total absence of lesions in such rabbits whenever sacrificed (2 to 80 days). Reduction of BAL to $\frac{1}{2}$, and even to $\frac{1}{3}$, of the lower optimal dose still results in considerable to slight diminution of the renal cortical damage, complete absence of lesions in groups of cortical convoluted tubules, and permits considerable regeneration of damaged but not completely destroyed tubules. Optimal dose therapy beginning at 30 minutes results in diminution or entire absence of damage to a considerable proportion of the renal cortical parenchyma, and, after 1 hour, in sparing of at least some. Residual damage in late sacrificed surviving rabbits consists of focal areas of cortical atrophy, corresponding in extent to the degree of initial necrosis.

The clinical and pathologic effects of the vesicant nitrogen and sulfur mustards. IRVING GRAEF, DAVID A KARNOFSKY (by invitation), VAL B JAGER (by invitation), HOMER W SMITH (by invitation), *Dept of Pathology, New York Univ College of Medicine, New York*. The toxicity,

clinical and pathological effects of di-B-chloroethylmethylamine were appraised in mice, rats, rabbits, dogs, chickens and pigeons by administering the agent as a gas, or as a liquid, cutaneously, orally, subcutaneously, intraperitoneally, and intravenously. Di-B-chloroethylmethylamine is qualitatively similar in effects to di-B chloroethylethylamine, di-B-chloroethylpropylamine, tri-B-chloroethylamine and di-B chloroethyl-ethylsulfide.

These compounds have a necrotizing action on contact with skin, cornea or mucous membranes, on inhalation, injury to the respiratory passages, and on ingestion, lesions in the mouth and upper gastro-intestinal tract result. The agent is readily absorbed from skin and mucous membranes. In mammals the intravenous LD₅₀ varies from 1 to 3 mg/kg, birds are considerably more resistant.

By various routes of administration, the pattern of systemic effects is essentially similar. Supra-LD₅₀ doses produce neurologic symptoms and death within 24 hours. After LD₅₀ doses, animals may remain almost asymptomatic for 1 to 2 days. This is followed by anorexia, weight loss, diarrhea and prostration, and death occurs in 3 to 6 days. Animals surviving injury usually recover completely. Lymphocytopenia and granulocytosis occur within 12 hours after exposure, followed by progressive severe leucopenia for 3 to 4 days. The erythrocyte count is little affected.

These clinical events are paralleled by (1) abrupt atrophy of lymph nodes, spleen and thymus, due to lymphocytopenia, (2) aplastic degeneration of the bone marrow in 2 to 3 days, and (3) degenerative changes in the mucosa of the small intestine.

These clinical-pathological effects resemble those induced by X-ray irradiation.

Studies on pyridoxine deficiency in Rhesus monkeys. LOUIS D. GREENBERG (by invitation) AND JAMES F. RINEHART *Divisions of Pathology and Pharmacology, Univ. of California Medical School, San Francisco*. Two and five-tenths to 3 kilogram Rhesus monkeys were placed on a modified M-3 diet (Waisman et al., Arch. Biochem. 4: 260, 1944) supplemented with synthetic water soluble vitamins, vitamins A and D and mixed natural tocopherols. The supplement included synthetic "folic acid" and biotin but no pyridoxine. On this regime animals began to lose weight after 10-14 days and have continued to show progressive loss of weight and decreased food consumption during the 87 day period of observation. Their activity and strength were also reduced.

Weekly or bi-weekly studies of the blood picture have revealed thus far the development of a mild microcytic anemia while the blood picture in control monkeys has remained almost constant. The experiment is still in progress and to the present time no signs of dermatitis or neurological

manifestations are evident. [Aided by a grant from the Christine Breon Fund for Medical Research of the Univ. of California. We are indebted to Lederle's Lab., Pearl River, New York, for the synthetic "folic acid".]

Oxidized cellulose absorption and histopathology. O. M. GRUNZIT *Division of Pathology and Pharmacologic Toxicology, Research Labs., Parke, Davis and Company, Detroit, Mich.* Oxidized cellulose (Oxycel) is an acidic substance, a polyanhydroglucuronic acid complex. In contact with weakly basic solutions it forms water soluble salts. The physical appearance and structure of oxycel is similar to ordinary cotton or cotton gauze. In contact with tissues or tissue fluids, oxycel forms a coagulum, absorbs fluids and swells, producing a local hemostatic effect. The influx of basic substances from body fluids neutralizes the acidic oxycel and forms soluble and absorbable degradation products. In the initial stages of lysis and absorption, the oxycel becomes a dark colloidal mass which on further influx of fluids becomes water-thin in consistency. The lysis and absorption of oxycel from tissues takes place in 3 to 14 days, depending on the size of the implant and the vascularity of the tissue bed. The formed tissue coagulum limits the extent of tissue reaction to oxycel implant. The amount of coagulum formed determines the type of initial lesion, either a thin or thick walled cyst, a nodule, or a loose trabeculated mass. Coagulum formation between adjacent surfaces of tissues leads to formation of adhesions. It is the main cause of subsequent tissue reaction in the process of its absorption. A massive phagocytic cell invasion occurs, followed by granulation tissue formation. The oxycel constitutes a soluble, absorbable surgical gauze and possesses at the same time, local hemostatic properties. Its reaction with tissues is relatively mild and limited in area. The resultant protein coagulum constitutes residue, and its absorption determines the rate of healing with formation of scar tissues.

The selective radiation of specific tissues and viscera by means of radioactive isotopes. P. F. HAHN and C. W. SHEPPARD (by invitation) *Dept. of Biochemistry, Vanderbilt Univ.* Malignant diseases which are radiation sensitive may frequently be treated by the use of artificial radioactive isotopes where X-radiation fails due to inaccessibility of the tissue to the directed beam of the latter type of radiation. Because of the wide variety of isotopes available, one may deposit the desired radiation emitter in selected tissues, depending on the use of the correct chemically or biologically reacting element. The form in which the compound is administered may also be used to assist in directing its subsequent course in the body. The route of administration may be varied in order to obtain selectivity. A wide choice of radiation spectra is

available in the use of isotopes permitting some control of the depth of penetration of the rays

Deep-seated, hollow viscera may be subjected to radiation by the employment of insoluble suspensions of isotopes. Radiation sickness is not an accompanying common feature of such treatment. This is attributed to the fact that destruction of normal tissue which occurs in X ray therapy under these conditions is minimized. Furthermore, the rapidly decreasing intensity of tissue ionization at increasing distances from the source of radiation works in favor of the therapist rather than against him. [This work was done under a grant from the Nutrition Foundation.]

Effect of biotin and other B vitamins on proteinases. NELLIE HALLIDAY¹ (by invitation) and CHARLES WEISS² *Research Labors, Mt Zion Hospital, San Francisco*. Biotin exerts a procarcinogenic effect (du Vigneaud et al.) and influences susceptibility to malaria (Trager). It is present in high concentration in vaccine virus. In common with others of the group of the B vitamins it stimulates the growth of various microorganisms and animals. Because the endocellular proteinases (cathepsins) are concerned with protein synthesis and growth, we looked for a possible effect of B vitamins upon these enzymes. Colchicine was included since it arrests cell division.

Method. The experimental procedures have been described (Weiss and Halliday). The vitamins and colchicine were dissolved in distilled water, adjusted to about pH 4.9 and employed in varying concentrations per cc of test solution, as follows:

Test material	Concentration—range
Thiamine	400 to 4×10^{-4} γ
Riboflavin	40 to 4×10^{-4} γ
Calcium pantothenate	800 to 8×10^{-4} γ
Niacin	2 to 2×10^{-4} mg
Biotin	0.75 to 3×10^{-4} γ
Inositol	3 to 3×10^{-4} mg
Colchicine	1.2 to 1.2×10^{-4} mg

Cathepsin II from beef spleen, and papain, purified by the method of Greenberg and co workers were incubated 2 hours with test material in the presence of cysteine and buffer solution before the substrate, benzoyl-L-arginineamide (BAA), was added and titrations begun, according to method of Fruton and Bergmann.

Results. With the exception of inositol which caused a slight inhibition, neither the vitamins nor colchicine had any significant effect on the enzymes employed. Since B vitamins when phosphorylated and linked with protein form oxidative, respiratory, decarboxylase or dehydrogenase systems, their effect on growth is apparently referable to these rather than to the proteolytic enzymes.

Tissue lipids in essential xanthomatosis. ARILD E. HANSEN and HILDA T. WIFSE (by invitation) *Dept of Pediatrics, Univ of Texas School of Medicine, Galveston*. The fatty acids in the lipid fractions and cholesterol (total and ester) were determined in the tissues of a 3 year old child who suffered from marked essential xanthomatosis and the results compared with those of control subjects. The histologic features of the tissues were consistent with a reticuloendotheliosis of the Hand-Schüller Christian type. The quantity, distribution, and degree of unsaturation of the fatty acids in the acetone insoluble (phospholipid) and acetone soluble (cholesterol ester plus triglyceride) fractions as well as the total and esterified cholesterol were essentially the same in the kidney, spleen, and pancreas. The amount of triglyceride fat in the liver, subcutaneous fat depots, and skin were rather small but of questionable significance. There was a decreased quantity of cholesterol and cholesterol esters (0.53 and 0.29% respectively) in the adrenal gland compared with that of the control (3.73 and 2.68% respectively). The cholesterol ester fatty acids comprised 2.4% of the total fatty acids in contrast to 22.0% for the control. In the case of the pathologic marrow substance, a reverse situation existed. Over 80% of the fatty acids in the involved marrow tissue was cholesterol ester fatty acids whereas in the control this was only 0.7%. The iodine number of the acetone soluble fatty acids in the diseased marrow tissue was greater than that found in the normal marrow. The degree of unsaturation of the fatty acids was not great enough to be consistent with the presence of highly unsaturated fatty acids. [This study was aided by grants from the National Live Stock and Meat Board and the Medical Research Fund of the Graduate School, Univ of Minnesota.]

Prevention of experimental arterial lesions by cholesterol. RUSSELL L. HOLMAN *Dept of Pathology, School of Medicine, Univ of North Carolina, Chapel Hill*. Many of the recent publications regarding cholesterol atherosclerosis in rabbits postulate that a primary injury to the vessel wall precedes the deposition of lipid. Several of the textbooks of pathology suggest a similar sequence for man. The terms "lipoidal degeneration" and "lipoidal infiltration," however, continue to dominate discussions of pathogenesis, and the role of cholesterol and its esters in arterial disease remains a controversial subject.

In previous communications to this society it has been shown that arterial lesions affecting principally the inner layers of the large arteries can be produced with regularity in dogs by controlling two factors, diet and renal insufficiency. The "dietary factor" is concentrated in (but not unique to) commercial cod liver oil, is heat stable, is not readily oxidized, is not vitamin A, and is not

¹ University of California Dept of Pediatrics

² Laboratories of Jewish Hospital Philadelphia 41

vitamin D The method by which renal insufficiency is produced (uranium nitrate, mercuric chloride, bilateral nephrectomy, *Lepidospira canicola*) is relatively unimportant, but some degree of renal damage is essential

In the acute stage the lesions resemble those of periarteritis nodosa or rheumatic arteritis Some of the lesions have healed leaving insignificant scars, while some of the more conspicuous scars resemble "spontaneous" lesions in this species

The lesions are aggravated by repeated injections of homologous plasma, are not affected by choline, but are retarded or prevented by vitamin E and, to our surprise, by cholesterol

While much more control data is needed, the unanticipated finding that cholesterol protects against these arterial lesions raises the question Could cholesterol and cholesterol ester be primarily protective and only secondarily alternative? (*This work was aided by a grant from The John and Mary R Markle Foundation The Vitamin E was supplied by Distillation Products, Inc*)

Experimental jugular phlebitis W C HUEPNER *Warner Inst for Therapeutic Research, New York* Two series of 5 dogs each were used in experiments directed at the production of a chronic phlebitis of the jugular veins In one series the tips of the eye teeth of one side were amputated and the tooth canals were injected with 24-hour cultures of hemolytic streptococci Roentgen-pictures taken one and two months later showed abscess formation of the upper eye teeth of two dogs, while blood cultures made four and five months after the tooth resections showed once in these two dogs the presence of gram negative, anaerobic bacilli, possibly related to *Clostridium Welchii* The histologic examination of the neck vessels performed 8 months later revealed tongue-like endothelial proliferations in the external jugular vein of one of the two dogs with abscessed teeth The external and internal jugular veins of the 5 dogs of the second series were ligated and five months later 0.5 cc of a bouillon culture of the bacilli obtained from the blood of the 2 dogs of the first series was injected into a vein of the hind leg The external jugular veins of 3 of these 5 dogs showed after 8 months not only definite cushion-like or tongue like proliferation of the endothelium, but in one instance also several granulomatous intimal foci and medial hypertrophy The experimental observations support clinical evidence concerning the possible existence of latent jugular phlebitis as the result of toxinemias and allergic reactions to abscessed teeth and tonsils, and point to the potential therapeutic importance of such venous lesions

Studies on the mechanism of production of systemic injury by di-B-chloroethylmethylamine hydrochloride DAVID A KARNOFSKY (by invitation), IRVING GRAEF, and HOMER W SMITH (by

invitation) *Dept of Pathology, New York Univ College of Medicine, New York* 1 By occluding the circulation to the legs of rats and rabbits for 2 to 5 minutes, by a clamp placed on the aorta and vena cava immediately before the intravenous injection of 1 to 1.5 LD₅₀ doses of di-B-chloroethylmethylamine hydrochloride, the femoral bone marrow was protected and became hyperplastic, whereas the marrow cephalic to the clamp was destroyed The hyperplastic marrow was capable of maintaining a normal or elevated leucocyte count during the usual 4 day survival period This demonstrates that the leucotoxic action of the agent is rapid and direct, that animals may be fatally intoxicated in spite of the prevention of leucopenia, and that marrow spared from the direct action of the agent continues to flourish

2 Occluding the circulation for 5 minutes to a portion of the small intestine just prior to and during the intravenous injection of 1 to 1.5 LD₅₀ of the agent, protected that portion of the intestinal mucosa, whereas characteristic degeneration occurred in the rest of the intestine The direct rapidly completed action of the agent on the intestinal mucosa was thus demonstrated

3 Permanent ligation of the biliary duct 3 days prior to the injection of the agent, did not alter the intestinal lesions after parenteral injection

4 The possibility that the lymphocytotoxic effects were due to adrenal cortex stimulation ("alarm reaction") was also investigated In adrenalectomized rats, the parenteral injection of the agent caused lymphocytic fragmentation almost as extensive as in the non-adrenalectomized rats This suggests that this agent has a direct lymphocytotoxic effect

Influence of single doses of alpha tocopherol on growth and testicular atrophy of rats HANS KAUNITZ (introduced by H P Smith) *Dept of Pathology, College of Physicians and Surgeons, Columbia Univ, New York* In co-operation with Pappenheimer and Schogoleff, it was observed that the onset of testicular atrophy of rats on an Evans Burr diet was retarded by a single dose of alpha tocopherol administered on the 15th day It seemed interesting to investigate whether the well studied growth retardation of rats on tocopherol low diets could also be influenced by single doses of tocopherol on the 15th day

A colony was grown on a yeast free diet supplemented by essential vitamins, developed in co-operation with Dr Charles Slanetz, its tocopherol content, examined with the Emmerie-Engel reagent by the Kaunitz-Beaver method, was below 3 mgs per 100 grams One group received no supplement, the other was given single doses of alpha tocopherol, from 1 to 27 mgs, on the 15th day

The weight deficits of male animals were calculated below the curve of optimal growth, after

Zucker and Zucker The results proved that after the 7th week, the protected animals grow significantly better than the unprotected group. A less pronounced but similar result was found in rats kept on Evans Burr diet.

The rats on yeast free diet showed, as those on Evans Burr diet, definite delay of the testicular atrophy after a single dose of tocopherol on the 15th day. Many animals with testicular atrophy had no growth deficit. This suggests that the influence of tocopherol on growth is dissociated from that on the testicular atrophy. [Aided by a grant from the John and Mary R. Markle Foundation.]

The pathogenesis and pathology of experimental air-borne influenza. A virus infection in mice. CLAYTON G. LOOSLI, Dept of Medicine, Univ of Chicago, Chicago, and the Commissions on Influenza and Air-Borne Infections, Army Epidemiological Board, Office of the Surgeon General, A U S Influenza. A Virus infections were produced in mice by allowing them to breathe atmospheres containing the virus. The mice were then killed at close intervals of time up to three and one half months after exposure and the respiratory system studied grossly and microscopically.

Grossly, pulmonary lesions appeared after the third day of exposure as red edematous pin point areas, which progressed in size and coalesced to involve up to 80 per cent of the lung tissue in some of the surviving animals. Influenzal pulmonary lesions were present in all the animals killed up to three and one half months after exposure.

Microscopically, the upper air-passages (nasal and pharyngeal epithelium) appeared to be essentially free of involvement. Lesions were first seen at 48 hours as focal areas of degenerating epithelial cells lining the trachea and bronchi. These became progressively more extensive to involve the major portion of the trachea and all the bronchi of the involved lobes by the sixth day. At the third day focal areas of inflammation appeared in the alveolar spaces, and in the walls of the bronchi. The exudate was characterized by edema fluid, a few polymorphonuclear leucocytes and hematogenous mononuclear exudate cells. The alveolar walls showed essentially no involvement. At the sixth day the bronchial epithelium began to regenerate, became hyperplastic, and produced obstruction of some of the bronchi and a permanent atelectasis of the whole or portions of the involved lobes. The hyperplastic bronchial epithelium grew into the collapsed tissue and underwent hyaline degeneration resulting in cyst-like spaces lined by cuboidal epithelium.

Experimental non-bacterial cardio-vascular inflammation. WARD J. MACNEAL, ANNE BLEVINS (by invitation), ALICE E. SLAYKIN (by invitation) and HELEN SCANLON (by invitation). Dept of Bacteriology, New York Post-Graduate Medical

School and Hospital, Columbia Univ. Since June 1943, we have observed a disease in rabbits, guinea pigs and mice, characterized by benign course and by irregularly disseminated lesions of cardiac valves, mural endocardium, myocardium, pericardium, pulmonary and aortic arches and small vessels in lung, capable of transmission by injection of blood. To demonstrate the lesions the animal is sacrificed one to three weeks after inoculation and promptly fixed by vascular perfusion. Many sections are searched for the lesions, in which mitotic figures indicate activity.

Injection of pericardial fluid from 5 patients with unquestioned rheumatic carditis has been followed in each instance by this experimental disease and it has been propagated to the 15th animal in series.

Injection of citrated blood from 6 young persons with severe active rheumatic fever has given positive result in some animals for each specimen.

Blood from 16 other patients with cardiac damage, slight fever and abnormal sedimentation rate has given less uniform results.

The supposed viruses have been propagated in embryonated eggs, in one instance through 25 serial transfers, followed by transfer back to mammals.

The disease can be mimicked by multiple injections of incompatible blood or by single large injection of influenza virus. Serial transmissibility should distinguish. Apparently, also, there are several natural viruses in small animals, not so easily differentiated and possibly one or more of these may occur naturally in rodents and in children.

Possible relation of these viruses to human rheumatic diseases seems to be worthy of further study. [Aided by Grant No. 540 of the Council on Pharmacy and Chemistry, American Medical Association and by the Virus Research Fund of the Lambert Pharmacal Company.]

Liver function tests from a surgical point of view. STEPHEN MADDOCK, M.D. and DOROTHY JENSEN, A.B. (by invitation). *The Surgical Research Laby, Boston City Hospital, Boston, Mass.* For the past ten years the majority of liver function tests in this hospital have been performed in this laboratory. Over that period it has become increasingly obvious that the use of liver function tests in all cases requiring biliary tract surgery are of great value from the standpoint of the care of the patient.

In surgical practice it is important that the tests be relatively simple and rapid. The tests employed are Icteric Index, Urobilinogen, Hippuric Acid Excretion, Alkaline Phosphatase, Prothrombin Time, Cephalin Flocculation and Bromsulphalein.

The important differential diagnosis lies, of course, between mechanical obstruction, amenable to surgery, and all other types of jaundice.

In this presentation no attempt will be made to analyze the large mass of data but rather to present certain patterns which usually can be relied upon preoperatively

The patient upon whom biliary tract surgery is contemplated should receive the above tests. Often what appears to be a case requiring simple cholecystectomy may need several weeks of careful preparation in order to insure an uneventful convalescence

Every patient with biliary obstruction is entitled to exploratory laparotomy. In frank obstruction, operation should be performed as quickly as possible after the diagnosis is established

Ischemic and anoxic damage to myocardial capillaries and its relation to shock, angina pectoris and myocardial infarction. G. R. MINIFF, MILDRED STAHLMAN, F. R. McCRICK, L. E. SMITH and H. J. SMITH, JR. (introduced by E. W. Goodpasture) *Dept. of Medicine, Vanderbilt Univ. Medical School, Nashville, Tenn.* In the Bayley-LaDue heart preparation a ligature under a branch of the anterior descending coronary artery may be tightened to occlude the artery. An exploring electrode placed over the ischemic area sometimes revealed progressive myocardial damage after the artery had been released and blood flow to the ischemic part reestablished. Unless elements other than myocardial ones participated, this effect was inexplicable. It was possible to show that ischemia or anoxemia of sufficient duration results in extensive capillary endothelial damage demonstrable by permeability to trypan blue. Extensive and irreversible myocardial damage may well be secondary to this capillary injury rather than directly due to the effect of ischemia upon the muscle fibers themselves. The relation of coronary artery spasm to myocardial infarction, Wigger's cardiac factor in irreversible shock, and the frequent occurrence of myocardial infarction without demonstrable coronary occlusion could be explained on the basis of ischemic or anoxic myocardial capillary endothelial damage. The evidence indicates this damage may lead to irreversible myocardial injury despite reestablishment of coronary circulation or oxygenation and suggests that an important factor is the duration of the insult, that a critical time exists for development of irreversible cardiac damage. [Supported in part by a grant from Ciba Pharmaceutical Products, Inc.]

Effect of the leukocytosis-promoting factor of exudates on human beings. VALY MENKIN, E. ULLED (by invitation), and E. G. GOODMAN (by invitation) *Dept. of Pathology and Medicine, Duke Univ. School of Medicine, Durham, N. C.* The earlier studies by one of the authors (V. M.) have demonstrated the liberation in inflammatory exudates of a protein-like substance associated with the pseudoglobulin fraction of exudates capable of increasing the number of circulating leukocytes

and of inducing a hyperplasia of granulocytes and of megakaryocytes in the bone marrow. This substance offers a reasonable explanation for the leukocytosis accompanying numerous inflammatory processes.

This fraction, active on dogs and guinea pigs, has now been found to increase likewise the number of circulating leukocytes in human beings. A canine fraction of leukocytosis promoting factor has been used. The rise in white count with potent fractions ranges from about 80 to 150 per cent. The material is both innocuous and rapidly active on human beings, and therefore may be of definite clinical significance.

Observations on Tyzzer's disease of mice. F. L. RIGHTS (by invitation), E. B. JACKSON (by invitation) and J. E. SWADEL *Division of Virus and Rickettsial Diseases, Army Medical School, Washington, D. C.* An enzootic disease was encountered among certain stocks of white mice (Swiss), which presented a picture indistinguishable from that observed by Tyzzer in 1917 in Japanese waltzing mice. The present malady, like the original, was transmitted irregularly when affected liver tissue was injected intraperitoneally into normal mice. However, such inoculum induced a fatal encephalitis in mice injected intracerebrally. Furthermore, the infection was experimentally maintained by serial passage of brain material for over a year. The cerebral lesions, like those found in the livers of naturally infected mice, consisted of a central area of necrosis usually surrounded by a zone of polymorphonuclear cells. The long thin banded, pleomorphic, gram negative, non-motile rod which Tyzzer named *Bacillus piliformis* occurred in abundance in infected brains. This organism which was constantly associated with infectious material did not grow on a number of the plain or enriched media but multiplied readily in agar slant tissue cultures containing chick or mouse embryo cells. It rapidly lost its virulence for mice when grown under these conditions.

Rats, hamsters and rabbits succumbed with this experimental encephalitis.

Amino acid utilization in simultaneous hypoproteinemia and anemia. Elimination of one essential from growth mixture (Rose). F. S. ROBSCHT, ROBBINS, and L. L. MILLER (by invitation) *Dept. of Pathology, School of Medicine and Dentistry, Univ. of Rochester.* A mixture of pure crystalline amino acids essential for growth in rats (Rose) is well utilized to form both hemoglobin and plasma protein in a doubly depleted dog (simultaneous hypoproteinemia and anemia). Elimination of threonine, methionine or phenylalanine alters efficiency of utilization of the amino acid mixture as manifest by urinary nitrogen excretion. The output of both hemoglobin and plasma protein for a time is well sustained.

The significance of hyperemia around tumor

implants WARNER L SHIDON (by invitation) and DALE R COMAN *McManus Lab of Pathology Univ of Pennsylvania, School of Medicine, Philadelphia* Intense local hyperemia is a constant finding in the vicinity of transplantable mouse tumors. Experiments were directed toward determining the significance of this phenomenon. It was found that hyperemia appeared within 18 hours after implantation and was progressive thereafter so long as the tumor grew. Implants of homologous adult muscle tissue failed to produce hyperemia indicating that the hyperemia observed in the preceding experiment was not caused merely by the presence of foreign tissue. Heterologous tumor implants did not produce hyperemia showing that the vascular response did not depend upon the fact that the tissue was neoplastic. Homologous embryonic tissue, which grew for a time in the host, excited strong hyperemia that faded as the embryonic tissue finally regressed. This suggested that the hyperemia was due to the presence of proliferating cells. This hypothesis was tested further by the following experiment. Tumor 1, from Bigg albino mice, when implanted in C57 mice grows for a time and then regresses, leaving the mice resistant to subsequent implants of this tumor. It was found that the initial implants of Tumor 1, during their short growth period produced hyperemia, whereas subsequent implants of the same tumor in the same mice did not grow and did not cause hyperemia.

It is concluded from these experiments that the hyperemia around transplanted mouse tumors is due to the presence of proliferating cells. This increased flux of blood presumably operates advantageously to the dividing tumor cells. Hyperemia is the first apparent step in the process by which the tumor establishes its own blood supply.

Studies by radioactive methods of the distribution, retention, and excretion of colloidal particles administered intravenously in humans C W SHEPPARD (by invitation) and P F HAHN *Dept of Biochemistry, Vanderbilt Univ* Colloidal sols of manganese dioxide containing radio active manganese have been administered successfully to humans by the intravenous route. In cases suffering from fatal, malignant diseases, autopsy findings indicated that the particulate matter was retained by phagocytosis. Distribution was found to show a rough correlation with the reticulo-endothelial system. Release of the material from the body is found to be relatively slow but, nevertheless, at an appreciable rate. This was further substantiated by gamma ray measurements. Excretion of the material was found to be predominantly through the stools. [This work was done under a grant from the Nutrition Foundation.]

The permeability of renal glomeruli for proteins in lower animals HANS F SNETANA *Dept of*

Pathology, College of Physicians and Surgeons, Columbia Univ, New York, N Y While experimenting with the reabsorption of protein dye combinations by the "open" tubules of urodeles,¹ it was found that such protein dyes, injected intravenously, passed through the glomerular filter. Because of this unsuspected finding, a study was undertaken to follow the fate of various protein-dye preparations after intravenous injections into mammals. *Procedures* Solutions of peptone, egg albumin, serum albumin, serum globulin and casein were coupled with the disodium salt of 2 naphthol 3,6 disulfonic acid (R salt) according to methods described by Kabat and Heidelberger.² These protein R salt combinations are quite stable and can easily be identified by their intense red color. Series of mice, rats, guinea pigs, rabbits and dogs were injected intravenously and their organs were studied from half an hour to thirty days after the injection.

Results In mice and rats, tiny, brilliantly-stained red granules appeared in the lining cells of the convoluted renal tubules after about one hour following an injection of 0.5 cc of heterologous as well as homologous protein dye preparations, and they became more abundant after several days, after one month they had almost entirely disappeared. Colored matter was present in the reticulo-endothelial cells of most viscera.

No passage of protein dye combinations through the glomerular filter and reabsorption by tubules was observed in guinea pigs, rabbits and dogs.

Thymic atrophy (accidental involution) and its failure to occur in calcium deficiency HERBERT STOERK (introduced by H P SMITH) *Dept of Pathology, College of Physicians and Surgeons, Columbia Univ, New York* A series of observations indicated that thymic atrophy occurred with body weight deficit which was induced by inanition, restricted feeding or single deficiencies. The extent of the atrophy in most cases roughly paralleled the amount of body weight deficit. As reported previously (*Proc Soc Exp Biol and Med*, 56: 151, 1944), pyridoxine deficiency had a most striking and apparently specific effect in producing thymic atrophy, far beyond the expected atrophy for the body weight deficit. An opposite effect of apparently specific nature has been observed in rats maintained on diets low in calcium. The thymus of rats on a diet very low in calcium but otherwise adequate, in spite of growth retardation and even body weight loss, were not smaller than those of normal animals of the same body weight and were much larger than the glands of controls on the

¹ Smetana, H F and Johnson F R, *Am J Path* 18: 1029 1942

² Kabat E A and Heidelberger, M, *J Exper Med* 66: 229 1937

same caloric intake but receiving normal amounts of calcium. Such failure of the thymus to undergo accidental involution, as observed in adrenal or gonadal insufficiency, was termed by earlier observers "thymus hyperplasia." However, on proper comparison, neither of these two latter conditions

change the normal course of thymic development (*Endocrinology*, 31:329, 1941)

The described effect of low calcium feeding adds another condition to those in which the usual response of the thymus to harmful stimuli fails to occur

THE AMERICAN INSTITUTE OF NUTRITION

TENTH ANNUAL MEETING

Atlantic City, N. J., March 11, 12, 13, 14, 15, 1946

(For possible corrections in any of the following abstracts see the next issue)

Caloric intake and the utilization of dietary protein for growth. DAVID K. BOSSHARDT (by invitation) and RICHARD H. BARNES *Dept. of Biochemical Research, Sharp and Dohme, Inc., Glenolden, Penna.* It has been shown previously that a restriction of protein intake resulting from the feeding of a diet containing a small percentage of protein or by restriction of the entire diet through paired-feeding causes a decrease in the utilization of protein for growth. It is probable that the major factor causing decreased protein utilization under these conditions is the level of protein consumed. However, another factor that is common to both of the above conditions and may be involved in the lowered protein utilization is a decreased caloric intake.

Caloric intake and protein utilization have been compared in growing rats and mice that were consuming isocaloric diets *ad libitum*. Protein utilization was measured as the percentage of absorbed protein nitrogen used for body nitrogen gain and caloric intake was calculated as the average daily consumption of calories per 100 cm² body surface area (with mice the calculation was based on weight^{2/3}) during the experimental feeding period. Four protein sources were fed to rats and 3 to mice. At least 7 levels of each test protein were included in the diets. With each protein source it was found that there was a maximal caloric intake per unit body size and that this highest intake was obtained at the level of protein in the diet that maintained maximal protein utilization. At levels of protein in the diet on either side of maximal protein utilization caloric intake decreased. A second series of studies has indicated that at any given level of protein intake, increases in caloric consumption may result in an improvement in the utilization of protein for growth.

Urinary excretion of riboflavin by college women. WILMA BREWER (by invitation), THELMA

PORTER, RUTH INGALLS (by invitation), MARIE DYI and MARGARET OHLSON *Dept. of Foods and Nutrition, School of Home Economics, Michigan State College, East Lansing.* The urinary excretion of riboflavin of fourteen college women was studied under the following conditions: (1) self selected diet, (2) usual diet supplemented daily with 3 mg of riboflavin, (3) controlled diet at six riboflavin intakes, and (4) 24 hour excretion after a 3 mg dose of riboflavin following each period of controlled intake. From three to nine subjects were studied at each of the following riboflavin intakes: 0.79, 1.04, 1.26, 1.62, 2.23, and 2.73 mg daily.

Urinary excretion of riboflavin on self chosen diets ranged from 144 to 850 mcg per 24 hours. The average urinary riboflavin for the last three days of each period of controlled diet was, respectively, 0.07, 0.16, 0.13, 0.32, 1.18, and 1.31 mg per 24 hours.

A study of the daily excretions and the excretion of the test dose after each dietary period indicated that 2.23 mg were in excess of the needs of the subjects. Four subjects showed a sharp increase in urinary excretion of the test dose after an intake of 1.26 mg and did not use additional vitamin to apparent advantage. For two subjects the data were incomplete but it appeared that the increase in excretion of test dose occurred between intakes of 1.26 and 1.62 mg. For four subjects the upper limit of intake which maintained tissue stores was not determined but an intake of 1.62 mg seemed to approach this point.

All of the subjects were in good physical health throughout the experiment.

The utilization of carotene from carrots by humans. ELIZABETH C. CALLISON (by invitation) and ELSA ORENT-KIELES *Bureau of Human Nutrition and Home Economics, U.S.D.A., Beltsville, Md.* Four young adults, ranging in age from 19 to 21 years, were maintained on a diet deficient in vitamin A, but adequate in other respects, until de-

fective dark adaptation appeared, as detected by the Hecht Shluer adaptometer

Quick frozen carrots were then fed as a source of vitamin A value, the amount necessary to restore and maintain normal vision being reached by gradually increasing the amounts of the vegetable fed

Both chemical and bioassay procedures were employed to determine the carotene content of the carrots. The bioassay value was found to be only a third of that determined spectrophotometrically, whereas in previous work with quick frozen peas and spinach, chemical and bioassay results had been in close agreement. When the vitamin A value of the carrots, determined by bioassay, was used as a basis for the calculations, the human requirement for vitamin A as supplied from carrots was very similar to that previously reported for certain green vegetables, e.g. peas and spinach. However, when the results of the chemical assay were used, the apparent human requirement was trebled in magnitude.

Thus it appears that carrots differ, from spinach and peas in the extent to which their carotene is utilized by two species of mammals, i.e. the rat and man. [This research was supported in part by an allotment made by the Secretary of Agriculture from Special Research Funds (Bankhead Jones Act of June 29, 1935)]

Relationship between protein intake and pyridoxine deficiency in the rat. Effect of supplementing a low-protein diet with methionine. LEOPOLD R. CERECEDO, *Dept. of Biochemistry, Fordham Univ., New York* 58, N Y (Read by title). Previous studies (Arch Biochem 5 207, 1944) showed that the level of protein in the diet has a pronounced effect on the severity of symptoms caused by a lack of pyridoxine in the rat. The acrodynia that developed on a low-protein diet (15 per cent casein, diet A) was a mild form in most cases, whereas in the animals receiving the higher protein levels (30 or 45 per cent), severe symptoms were produced. Further studies (Federation Proceedings 3 55, 1944) showed that rats receiving diet A supplemented with cystine (0.5 gm. added to 100 gm. diet) developed more severe symptoms and died sooner than those given diet A alone.

In the present study, rats of the Wistar strain were placed at weaning on diet A supplemented with methionine (0.31 gm. added to 100 gm. diet). The results were similar to those observed when cystine was the supplement. [Aided by a grant from the Committee on Scientific Research of the American Medical Association]

Storage of pantothenic acid in the mouse. LEOPOLD R. CERECEDO, JOSEPH G. SANDZA (by invitation) and EDWARD A. WHITE (by invitation). *Dept. of Biochemistry, Fordham Univ., New York*

58, N Y (Read by title). Litters of albino mice were placed at weaning on a ration consisting of purified casein 25, sucrose 53, salts 5, Crisco 10, lard 5, and Ruffex 2. Supplements of thiamine, riboflavin, pyridoxine, choline, alpha tocopherol, beta carotene, and vitamin D were added to the ration. One or more animals from each litter were killed at weaning, and the liver and muscles microbiologically assayed for pantothenic acid. Alopecia and cessation of growth were the first symptoms of pantothenic acid deficiency. The results indicate a relationship between the amount of pantothenic acid present in the liver and the time of appearance of the deficiency symptoms. The larger the amount of the vitamin in the liver, the longer was the period during which the animals grew and were free from alopecia.

Nursing mice and their progeny were placed on the above ration on the eleventh day of the lactation period. The young were weaned on the twenty-first day, and were continued on the deficient diet. The controls were young from mothers that had been given the stock diet during the whole lactation period. They were placed on the pantothenic acid free ration at weaning. The former were found to be more susceptible to the deficiency than the controls. This greater susceptibility showed itself as follows: they developed alopecia and ceased to grow at an earlier period, and their period of survival was much shorter. [This investigation was aided by a grant from the John and Mary R. Markle Foundation]

Strain differences in the resistance of rats to pyridoxine deficiency. LEOPOLD R. CERECEDO, *Dept. of Biochemistry, Fordham Univ., New York* 58, N Y (Read by title). The animals used in this study belonged to the Wistar and to the Sprague-Dawley strains. They were placed at weaning on a diet consisting of casein (Labco or Smaco) 50, sucrose 55, Crisco 5, cod liver oil 3, Osborne and Mendel salts 7. This ration was supplemented with the following vitamins, added per kilogram of diet: thiamine 10 mg., riboflavin 10 mg., and calcium pantothenate 40 mg. Resistance to the deficiency of pyridoxine was measured by (a) time of onset of the acrodynia, (b) the gain in weight during the experimental period, and (c) length of the survival period.

On the basis of the above criteria, the Sprague-Dawley rats were found to be more resistant to a lack of pyridoxine in the diet than the Wistar rats. The reason for the difference in susceptibility shown by the two strains is not known. However, several of the Sprague-Dawley rats were observed to eat their feces.

Previous studies in this laboratory (J. Nutrition 24 93, 1942; Arch Biochem 5 207, 1944) have shown that in the rat (1) the capacity to store pyridoxine, and (2) the protein level in the diet

influence the time of onset and the severity of the acrodynia produced by pyridoxine deficiency. The present study shows that a third factor, namely, the strain of rats used, should be taken into account when studying the biological action of this vitamin [Aided by a grant from the Committee on Scientific Research of the American Medical Association]

Relationship between salt intake and sweat salt concentration under conditions of hard work in humid heat JEROMI W CONN, MARGARET W JOHNSTON AND LAURENCE H LOUIS (by invitation) *Nutrition Laby, Univ of Michigan Medical School, Ann Arbor, Michigan* (Read by title) Fully acclimatized men living continuously in a simulated tropical environment and performing a standard amount of work each day (sufficient to produce 5 to 10 liters of sweat/24 h) respond to a diminishing salt intake by reducing the concentration of salt in the sweat, thereby conserving body salt. Down to surprisingly low levels of salt intake they are able to reestablish salt balance. On high salt intake levels much variation in sweat salt concentration among different individuals is observed. As salt intake is reduced, however, the concentrations of salt in sweat of different subjects on the same intake level approach each other. On very low levels of salt intake, individual variations in the limit of adaptability, i.e., production of sweat very dilute in chloride, determines whether

Subject	NaCl intake gms/day	Test period days	Avg sweat chloride conc * mEq/liter
D B	27	12	6
D B	27	23	5
K H	27	16	11
R L	19	6†	6
R L	19	10†	8
D B	19	19	5

* Average of daily determinations for each test period

† Consecutive periods

or not salt balance will be established [Work done under contracts with (1) The Office of Scientific Research and development, National Research Council, Washington, D C, and (2) The United States Army, Office of the Surgeon General, Washington, D C]

Attempts to produce a niacin deficiency in the monkey JACK M COOPERMAN (by invitation), KEITH B MCCALL (by invitation), W R RUEGGER (by invitation), and C A ELVEHJEM *Dept of Biochemistry, Univ of Wisconsin, Madison* Rhesus monkeys were given the basal ration (M-2) consisting of sucrose 73, casein 18, salts 4, cod liver oil 3, corn oil 2 and adequate amounts of ascorbic acid and the known B vitamins (including folic acid and biotin), except niacin, in an effort to produce a niacin deficiency. After 10 months on this niacin-low ration the animals began to lose weight and became anemic. Niacin at levels of 10 and 25 mg per day given orally or parenterally proved ineffective in correcting this syndrome. On the other hand, when the basal ration was supplemented with 3% whole liver powder, a good source of the monkey anti-anemia factor, the monkeys responded promptly both in weight gain and hemoglobin production. Apparently under these conditions the monkeys developed a deficiency related to the monkey anti-anemia factor.

When young monkeys were fed a ration in which corn grits were substituted for 40% of the dry M 2 basal they failed to grow and at the end of 2 months developed an anemia and a reversal in the neutrophil-lymphocyte ratio, symptoms typical of a deficiency for the monkey anti-anemia factor. The addition of niacin, tryptophane, or both to the ration proved ineffective in combating the deficiency. Supplementing the ration with 3% whole liver powder caused a rapid growth response and a prompt remission of the blood dyscrasia.

The biologically determined vitamin C potency of orange juice E W CRAMPTON and BARBARA W BURTON (by invitation) *Dept of Nutrition, MacDonald College (McGill Univ) P Quebec, Canada* Using a new biological assay procedure, in which the maximum development in height of the odontoblast cells of the incisor teeth of young guinea pigs is the criterion of potency, it has been shown that fresh orange juice and ascorbic acid fortified orange

Subject	NaCl intake gms/day	Test period days	Avg sweat chloride conc * mEq/liter
H B	18.5	20	30
L B (negro)	18.5	20	25
G J	18.5	19	35
G J	18.5	20	35
R L	18.5	11	12
D B	18.5	9	10
D B	18.5	22	18
K H	18.5	9	22
G C	18.5	38	40
H B	10.0	6	21
L B (negro)	10.0	6	14
G J	10.0	14	18
R L	10.0	12	8
D B	10.0	6	9
H B	5.5	4	13
L B (negro)	5.5	3	9
L B (negro)	5.5	10	9
G J	5.5	11	13
G J	5.5	5	10
G J	5.5	45	10
R L	5.5	11	7
R L	5.5	6	9
D B	5.5	14	8
K H	5.5	16	18
G C	5.5	21	24
L B (negro)	2.7	11	8
L B (negro)	2.7	10	6
G J	2.7	10	10
R L	2.7	10	5
R L	2.7	14	8

juice, but not "artificial" orange juice have a significantly higher vitamin C potency than is indicated by chemical assay of these materials. Parallel lots of pigs fed crystalline ascorbic acid at levels corresponding to the chemically estimated potencies of the juices were used as controls in all tests. The results suggest that orange juice contains some substance which enhances the utilization of the ascorbic acid present.

An unidentified factor or factors effective in the treatment of experimental blood dyscrasias in rats FLOYD S. DAFT and W. H. SENNELL, *Division of Physiology, National Inst. of Health, Bethesda 14, Md.* Anemia and granulocytopenia have developed in rats deprived of pantothenic acid (Pub Health Rep., 60:1201 (1945)). Despite the fact that the development of these dyscrasias could be prevented by the administration of adequate amounts of pantothenic acid, the results of therapy indicated that they were not signs of an uncomplicated deficiency of this vitamin. Granulocytopenia, unaccompanied by anemia, was corrected by the *L. casei* factor alone and there was evidence that at least a part of the anemic animals were deficient in this substance. It appeared, less conclusively, that rats with anemia alone or with both anemia and granulocytopenia might be deficient in one or more unidentified factors. Further investigations have yielded additional evidence which supports this point of view.

Weanling albino rats were given a pantothenic acid-deficient diet which was identical to the one previously employed except that it contained *L. casei* factor at a level of 4 micrograms per gram of food. Both anemia and granulocytopenia developed in high incidence in these rats. Treatment of affected animals with whole dried liver was considerably more effective than treatment with pantothenic acid. This suggests very strongly that at least one unidentified factor is required by the rat for the maintenance of normal levels of circulating blood cells.

Effect of excess nicotinamide on growth of the chicken W. J. DANN, *Dept. of Physiology, Duke Univ. School of Medicine, Durham, North Carolina* (Read by title). The addition of 0.1 per cent of nicotinamide to a growing mash for chicks did not affect the growth rate of chicks, 1.0 or 2.0 per cent caused a marked decrease in consumption of the mash and consequent decrease in growth rate. Control chicks on plain mash with food intake limited to that of the chicks receiving mash plus 2.0 per cent nicotinamide grew slightly better than the latter.

Commercial "day-old" chicks of several heavy breeds grew on the average 280 grams on the plain mash in 4 weeks, on mash plus 2.0 per cent nicotinamide *ad lib* they grew 125 grams in the same period. Their growth was not improved by adding 2.0

per cent of glycine or of choline chloride to the mash as well as the nicotinamide. Chicks given the mash with 2.0 per cent nicotinamide after 5 weeks had livers which were rather smaller, although a higher percentage of the body weight, than those of chicks fed plain mash. There was no difference between the weight of fat per gram of moist liver in the two groups, it was close to 7.5 grams for each.

The addition of 2.0 per cent of nicotinic acid to the mash had no effect upon food consumption or rate of growth. The same amount of glycine added also depressed food consumption and growth rate, but only to about one half the extent due to nicotinamide. [Aided by a grant from the John and Mary R. Markle Foundation.]

The effect of corn grits on the nicotinic acid excretion of the rat W. J. DANN, *Dept. of Physiology, Duke Univ. School of Medicine, Durham, North Carolina* (Read by title). It has been shown by Krehl and co-workers (Science 101:283 and 489 (1945)) that replacement of 40 per cent of a simplified basal diet containing 15 per cent of casein by corn grits inhibits the growth of rats, and that simultaneous addition of nicotinic acid or tryptophane reverses the inhibition. This effect has been confirmed, using a diet containing 15 per cent of Labco casein with Vanderbilt strain rats. Four-week growth of rats weighing 60 grams on the basal diet was 85 grams, on basal diet 60 parts plus corn grits 40 parts it was 40 grams, on the latter plus 10 mg. nicotinic acid per kilo, 71 grams. Groups of 9 rats were used.

The daily output of N¹-methylnicotinamide in the urine of 6 adult rats was followed. Three received the basal diet and excreted 150 to 200 micrograms daily, three others received the mixed basal diet plus grits and excreted 40 to 60 micrograms. After 10 days the diets of the groups were reversed, and the output of those changed from basal diet to the diet with grits fell to 40 micrograms daily, for 2 rats within 6 days, for the third only after 25 days.

The rats changed from the diet with grits to basal diet alone behaved very irregularly. The output of two fluctuated for the next month between 40 and 115 micrograms, ending at the low figure. The third steadily increased its output from 60 to 160 micrograms daily. This irregularity of response favors the hypothesis that the corn grits act indirectly by affecting the intestinal flora. [Aided by a grant from the John and Mary R. Markle Foundation.]

Absorption of radioactive iron by school children WILLIAM J. DARBY, PAUL F. HAHN (by invitation), RUTH C. STEINKAMP (by invitation), and MARGARET M. KASER (by invitation), *Depts. of Biochemistry and Medicine, School of Medicine, Vanderbilt Univ., Nashville, Tenn.* It is well established that the non-deficient adult male absorbs a negligible quantity of administered radioactive

iron (*J Exp Med* 69 759, 76 15) The uptake of iron is increased in the anemia of iron deficiency We have investigated the absorption of ferrous chloride tagged with the radioactive isotope by children 6 to 10 years of age in order to establish the iron absorption within this age group and, further, to ascertain whether a measure of this function might permit an estimate of the incidence of iron deficiency within a population of children

During the course of a nutrition survey 189 children were fed doses of 2.1 to 6.0 mg of iron as ferrous chloride Samples of venous blood were taken 10 to 15 days later and the radioactivity of the iron in the blood determined Assuming that all of the absorbed iron was combined as circulating red cell hemoglobin in the blood, the percentage absorption was calculated Simultaneously, determinations were made of hemoglobin concentration and various vitamin levels in the blood, physical examination and calculation of dietary intake from a one-week diet record were carried out

The mean percentage of iron absorbed was 13.5, the median, 11.5 Twenty-five per cent of the children showed less than 7.0 per cent uptake, seventy-five per cent, less than 17.0 per cent uptake These figures indicate a greater absorption than one observes in the adult male No correlation existed between hemoglobin levels and iron uptake by these children The hemoglobin levels *per se* appear to exert little effect upon the mechanism for control of iron absorption Little, if any, correlation existed between iron uptake and per cent of standard body weight, calculated daily iron intake, economic level of the group, or size of dose administered [This study was supported in part by grants from the Nutrition Foundation, Inc, the International Health Division of The Rockefeller Foundation, and the Tennessee Dept of Public Health]

Problems of world nutrition DAVID B DILL *Fatigue Laby, Harvard Univ, Boston, Mass* Those of us who have had an opportunity to observe first-hand the problem of providing an adequate ration for the peoples of Europe and Asia view with some concern the degree to which research in nutrition is devoted to the niceties of a perfectly balanced ration To Europeans and Asiatics the diets we define as essential for well-being exist only in a dream world

Reports indicate that the basic ration in central Europe is even less adequate than in Germany where the Potsdam agreement calls for a standard of living no higher than that of surrounding countries At the moment the official basic German ration calls for 1550 Calories with added points for workers Extra food can be had in the black market with enough money or barter On the other hand some do not get even 1550 Calories

It may be assumed that the greater the disparity in standards of living between America and the rest of the world, the greater the hatred of us thus en-

gendered With the techniques of modern war it is easy to visualize this hatred being fanned to flames which may consume us all

The members of this Institute, without neglecting the ills of our own nation, might well devote more of their attention to the staggering problems of world nutrition, defining goals adequate nutritionally and yet within the world's food productive capacity

Biotin deficiency produced by the feeding of Marfanil to rats GLADIS A EMERSON and J C KERFSZTFS *Merck Inst for Therapeutic Research and the Research Laby of Merck & Co, Inc, Rahway, N J* Manifestations of biotin deficiency were induced in the rat by the feeding of a purified diet containing 0.75% Marfanil The clinical picture appeared identical with that produced in rats consuming rations containing dried egg white The depletion signs consisted of sub-normal growth, alopecia and a generalized dermatitis The biotin avitaminosis could be prevented or cured by the administration of biotin P-aminobenzoic acid protected against weight losses but a mild degree of biotin deficiency (loss of the guard hairs) was seen The leucopenia and granulocytopenia occasioned by a lack of "folic acid" and the increased prothrombin time ascribable to a deficiency in vitamin K which occur following the feeding of sulfa drugs were not observed The coliform and total bacterial counts showed an initial decrease but returned to normal after 10 to 12 days on test

The effect of folic acid on the blood picture in human macrocytic anemia. GRACE A GOLDSMITH *Dept of Medicine, Tulane Univ School of Medicine, New Orleans, La.* Folic acid (synthetic L casei factor) was administered orally and parenterally to persons with pernicious anemia, sprue and nutritional macrocytic anemia The number of reticulocytes in the blood increased within 3 to 7 days after therapy was instituted following which there was a gradual rise in the percentage of hemoglobin and in the total erythrocyte count The hematocrit reading increased markedly in all instances When the initial leukocyte count was low this rose to normal during therapy and the percentage of granulocytes increased Improvement in the blood picture was accompanied by marked improvement in the general condition of the patient Folic acid had no effect on hematologic findings in either aplastic or familial hemolytic anemia Folic acid appears to be a potent anti-anemic factor for man and may be closely related to the erythrocyte maturing principle of liver which is effective in the treatment of pernicious anemia

Some effects of dietary oxalate on the teeth of white rats ¹ ROSS A GORTNER, JR (by invitation),

¹ The material in this article should be construed only as the personal opinion of the writer and not as representing the opinion of the Navy Department officially

J S RESTARSKI (by invitation) and C M MCCAY *Natal Medical Research Inst., Bethesda, Md* Previous studies have shown that limited amounts of dilute acid beverages (citric, lactic, phosphoric, etc.) of pH 2.6 cause gross damage to molars of rats within one week. Since oxalic acid is present in significant amounts in certain foods, experiments were undertaken to compare its effects with those of other acids on the teeth of rats.

Using oxalic acid solutions of various strengths, even the most acid (pH 2.1) failed to etch the enamel of rats drinking 20 ml daily for two weeks. Instead a thin, opaque deposit appeared over the exposed portions of the molars, being most prominent near the gingival margin on the lingual surfaces. Either oxalic acid or sodium oxalate, in the feed or drink, was capable of causing this encrustation. In general, the longer the animal received the oxalate and the greater the concentration, the greater the extent of deposit. In some respects this deposit grossly resembled human dental calculus.

When small amounts of oxalic acid or sodium oxalate were added to solutions of citric or phosphoric acids, the decalcifying properties of these acids, *in vivo*, was reduced. Orange juice had no effect on the teeth of rats over a two week period when the oxalate concentration reached approximately 0.10 per cent. A spinach diet, calculated to contain about 0.5 per cent of oxalic acid, formed no tooth deposit and was ineffective in protecting the teeth of rats from citric or phosphoric acid beverages, presumably because the oxalate was largely combined as insoluble calcium and magnesium salts.

The failure of skeletal calcification produced by high lactose diets and by simple caloric restriction. PHILIP HANDLER (introduced by W J Dann) *Dept. of Biochemistry, Duke Univ. School of Medicine, Durham N. C.* Weanling rats fed a standard "synthetic" ration in which the sucrose was replaced by lactose, galactose or glucose + galactose all died within 16 days. When similar diets were fed to somewhat older rats (initial weight 125 grams) they survived for several months but failed to grow. During this period they excreted an acid urine of extremely high calcium and phosphate content although serum calcium, phosphate, lactic acid and bicarbonate levels were all normal. Despite the abnormally great calcium absorption from the intestine, there was a complete failure of skeletal calcification. The following experiment was performed to determine whether this failure was the result of an inhibition of normal calcification mechanisms by circulating lactose or galactose or a non specific phenomenon associated with generalized growth failure. Two control groups were fed sucrose containing diets in which the salt mixture and cod liver oil were present in twice standard concentration and in one of which the protein concentration was also doubled. Then the food in-

take of both groups was restricted to one half that of the controls. Neither group gained any weight over a period of 6 weeks and in both groups there was almost complete failure of calcification.

Tissue lipids in child with chylous ascites maintained on low fat diet. ARILD E. HANSEN and HILDA F. WIESER (by invitation) *Dept. of Pediatrics, Univ. of Texas School of Medicine, Galveston*. A diet very low in fat, but otherwise adequate, was given to a 3 week old child with chylous ascites and continued until the age of 23 months. Clinical observations indicated that growth and development were quite satisfactory, however, he seemed more susceptible to respiratory tract infections and had more difficulty with the skin (prolonged impetigo, prickly heat, and eczematous patches) than the ordinary infant. There were no evidences of severe malnutrition although he never appeared to a robust child. Periodic fat absorption studies revealed that fat was not absorbed directly into the blood stream but accumulated in the peritoneal cavity. Serum lipid analyses showed essentially normal values for cholesterol, cholesterol ester, and the fatty acids in the acetone soluble and acetone insoluble fractions. The low iodine number of the fatty acids suggested that highly unsaturated fatty acids were not synthesized by this child. The patient died during anesthesia when an attempt was made to transfer the internal saphenous vein to the peritoneal cavity. Histologic study of the tissues was without significant findings, the kidney structure particularly showed no pathologic changes. Lipid analyses were made of the skin, body fat depots, muscle, and liver and the results compared with those of a 19 month old child who also died during anesthesia. No significant differences were found in the degree of unsaturation of the fat in the tissues examined in spite of the low iodine number of the serum fatty acids and the prolonged maintenance on a diet containing about one gram of butterfat daily. Tissue lipid analyses made on dogs subsisting on diets containing 0.13% butterfat and 28% of lard for relatively longer periods (6 mos. to 2 yrs.) showed differences in the degree of unsaturation of the fat in these same tissues. [This study was made possible by a grant from the National Live Stock and Meat Board.]

Ascorbic acid and dehydroascorbic acid in raw carrots as prepared for table use. ELIZABETH M. HEWSTON (by invitation) and ELSA ORENT-KEILES *Bureau of Human Nutrition and Home Economics, U.S.D.A., Beltsville, Md*. Because carrots are frequently eaten raw as strips or grated or shredded in salads, a study was made of the effect on the ascorbic acid content of different preparation procedures. These procedures involved varying the extent of carrot surface exposed to the air, the type and composition of the cutlery used, and the length of time the prepared carrots were held before serving.

Carrots were prepared in quarters and strips by means of plastic and stainless steel knives, in chips and strings by two types of stainless steel graters and in shreds by a plastic grater. Analyses were made immediately following preparation on some of the samples. Holding times of one hour were studied for all treatments and of three and five hours for the strings.

Ascorbic acid was determined by indophenol titration, "total" ascorbic acid following reduction with hydrogen sulfide, and dehydroascorbic acid by difference.

Results indicate that the amount of cut surface exposed to air is the most important of the factors studied in relation to retention of ascorbic acid. Conversion of reduced to dehydroascorbic acid at cut surfaces is almost instantaneous following by a slow oxidation of dehydroascorbic acid with time. [This research was done as part of a project supported by an allotment made by the Secretary of Agriculture from Special Research Funds (Bankhead-Jones Act of June 29, 1935)]

Hand sweat values in the calculation of chloride and nitrogen balance under conditions of hard work in humid heat. MARGARET W. JOHNSTON, JEROME W. CONN, LAURENCE H. LOUIS (by invitation) and BETTY F. STEELE (by invitation). *Nutrition Lab., Univ. of Michigan Medical School, Ann Arbor, Michigan* (Read by title). In men fully acclimatized to humid heat and working sufficiently hard to produce 5 to 10 liters of sweat/24 h, reasonably accurate balance studies for chloride and nitrogen can be made when the averages of the daily concentrations of these substances in hand sweat are used to represent their concentrations in total body sweat for the period.

Chloride Balance Given sufficient chloride in the diet to insure chloride equilibrium under the conditions outlined above one can predict what the average concentration of chloride in body sweat should be for the period studied by applying the following formula:

$$\frac{\text{Total chloride intake} - \text{Total urinary chloride}}{\text{Total sweat volume}}$$

When the predicted value for concentration of chloride in all of the body sweat produced in the period, is compared with the determined value (average of daily hand sweat chloride concentrations for the period) good agreement is obtained. The following are typical examples:

Period of study	Total sweat chloride conc predicted	Hand sweat chloride conc determined
days	mEq /liter	mEq /liter
17	42	43
3	41	39
13	16	15
10	23	24
9	19	17

Analyses for sodium indicate a parallel relationship.

Nitrogen Balance By the same reasoning the predicted value for the concentration of nitrogen in total body sweat for the period studied is obtained by means of the following formula:

$$\frac{\text{Total N intake} - (\text{Urine N} + \text{Stool N})}{\text{Total sweat volume}}$$

Agreement between the predicted and the determined value (average of daily hand sweat nitrogen

Period of study	Total sweat nitrogen conc predicted	Hand sweat nitrogen conc determined
days	grams/liter	grams/liter
6	0.55	0.59
7	0.47	0.46
5	0.27	0.29
9	0.25	0.29
13	0.42	0.45
15	0.32	0.29

concentration for the period) is good. [Work done under contracts with (1) The Office of Scientific Research and Development, National Research Council, Washington, D. C., and (2) The United States Army, Office of the Surgeon General, Washington, D. C.]

A study of the influence of various dietary deficiencies on the response of mice to the virus of Poliomyelitis. JAMES H. JONES, CLAIRE FOSTER (by invitation) and WERNER HENLE (by invitation). *Depts. of Physiological Chemistry and Pediatrics, Univ. of Pennsylvania, and Children's Hospital of Philadelphia, Philadelphia, Pa.* It has been shown previously that either a dietary deficiency of vitamin B₁ or partial starvation increased the resistance of mice to the murine adapted Lansing strain of poliomyelitis virus. By using the paired feeding technique it was found that the vitamin deficiency exhibited a greater protection than did the restriction of food intake, indicating that the effect of the vitamin deficiency could not be entirely due to the inanition.

Following these observations the effect of several other deficiencies, including that of the vitamin B₂ complex, protein, and tryptophane, has been studied. After fairly marked deficiency symptoms were manifest the animals were inoculated intracerebrally with an amount of virus that would produce paralysis and death in about 80% of the animals on a complete diet. In the case of each of the above three deficiencies total deaths were 80% or more within 28 days after inoculation when the experiments were discontinued. Incidence of paralysis varied from over 60% to more than 80%. Some of the deaths were due to the deficiencies as indicated by numerous deaths in corresponding groups on deficient diets but injected with a suspension of uninfected brain. There was no conclusive evidence

that a deficiency of the vitamin B₂ complex, protein, or tryptophane either significantly increased or decreased the resistance of mice to the virus of poliomyelitis [Aided by a grant from the National Foundation for Infantile Paralysis, Inc.]

Further observations on choline and related compounds in nutrition T H JUKES, A C DORN-BUSH (by invitation) and J J OLSON (by invitation) *Lederle Lab., Pearl River, N. Y.* The nutritional effects of various compounds related to choline were studied with chicks and with the "cholineless" mutant (No 34486) of *Neurospora crassa*

When compared with choline on a molar basis the activity of some of the compounds in promoting the growth of the *Neurospora* mutant was found to vary somewhat at different levels. The growth stimulating power of betaine, aminoethanol or methionine for this mutant was not increased by using combinations of aminoethanol and betaine, or aminoethanol and methionine

Thiamine in parboiled rice M C KIK *Univ of Arkansas, College of Agriculture, Fayetteville* Samples of rough rice were parboiled by boiling, steaming, soaking and steaming. The samples were dried, shelled, milled to approximately 10% bran removal and assayed for thiamine (B₁) (Expressed in micrograms per gram)

Boiling (5-10 min), B₁ 2.13-2.66

Steaming (10-30 min), at 5 lbs pressure, B₁ 3.00-2.57

Steaming (5-20 min), at 10 lbs pressure, B₁ 1.90-2.15

Steaming (5-20 min), at 15 lbs pressure, B₁ 2.70-2.45

Steaming (5-15 min), at 20 lbs pressure, B₁ 2.68-2.29

Soaking 15 hrs at room temp (27°) steaming (5-40 min) at 15 lbs pressure, B₁ 2.48-2.08

Soaking 45 hrs at room temp (27°) steaming (10-30 min) at 15 lbs pressure, B₁ 2.56-2.10

Soaking (2-36 hrs) at 35°C steaming 10 min at 15 lbs pressure, B₁ 1.70-3.60

Soaking (2-24 hrs) at 60°C steaming 10 min at 15 lbs pressure, B₁ 1.77-2.24

Soaking (1-6 hrs) at 70°C steaming 10 min at 15 lbs pressure, B₁ 1.17-3.20

Soaking 2 hrs at 70°C steaming (5-20 min) at 15 lbs pressure, B₁ 2.94-2.78

Soaking (0.5-3 hrs) at 80°C steaming 10 min at 15 lbs pressure, B₁ 2.20-3.60

Soaking (10-60 min) at 90°C steaming 10 min at 15 lbs pressure, B₁ 2.20-3.20

Soaking 6 hrs at 40°C steaming for 15 min at 15 lbs pressure (Malekized process) B₁ 2.00

According to rice conversion with vacuum B₁ 2.48 Without vacuum B₁ 2.35 B₁ was partly destroyed when exposed for over 20 min to 15 lbs pressure

Steaming of paddy greatly reduced breakage due

to shelling and bran removal [Aided by a grant from the Williams-Waterman Fund of Research Corporation]

Thiamine in soaked rice M C KIK, *Univ of Arkansas, College of Agriculture, Fayetteville* (Read by title) One hundred gram samples of rough rice (thiamine content 3.00 µg) and of brown rice (thiamine content 3.30 µg) were soaked for different lengths of time at room temperature (27°C) in 150 cc of distilled water and dried. Rough rice was shelled and these shelled rough rice samples and the brown rice samples were milled to approximately 10 per cent bran removal. All samples were assayed for thiamine. The results are presented below

Type of rice	Time of soaking	Average thiamine content	Loss of thiamine in steep water
	hours	µg / gram	per cent
Brown	0	0.44	
Brown	8	1.03	10.90
Brown	12	1.08	14.24
Brown	24	0.91	15.80
Brown	36	0.79	16.00
Rough	4	1.35	
Rough	8	1.03	1.30
Rough	12	1.12	4.04
Rough	16	1.50	
Rough	24	1.37	2.63
Rough	36	1.58	1.88

These data show that soaking of rough rice and brown rice has a favorable effect on the thiamine content of rice in the milled state

Rough rice soaked in water lost small amounts of its thiamine content in the steep water while losses for brown rice amounted up to 16.00 per cent after 36 hours of soaking [Aided by a grant from the Williams-Waterman Fund of Research Corporation]

The nutritional status of school children in Mexico City ERNEST E LOCKHART (by invitation), FRANCISCO DE P MIRANDA (by invitation) and ROBERT S HARRIS *Nutritional Biochemistry Lab., Mass Inst Technology, Cambridge and National Inst of Nutrition, Mexico* The nutritional status of 500 girls and 500 boys, 6 to 14 years old and living in the poorest district of Mexico City was measured. Blood cell volume, hemoglobin, plasma ascorbic acid, and serum albumin were estimated. The biomicroscope was used in an attempt to measure the extent of avitaminosis A and ariboflavinosis

43.5% were below 14 grams % hemoglobin, 33.7% were below 40% blood cell volume, 1.6% were below 4.0 grams % serum albumin, 38.4% were below 0.5 mgms % plasma ascorbic acid, 32% showed three or more arcades in the cornea, and 57% showed marked translucency of the conjunctiva

Compared with an earlier study (J Am Diet Assocn 19:182, 1943) on 760 middle class children

in Michigan conducted by the same research group and using the same techniques, the Mexican children show evidences of a superior nutritional status, except for hemoglobin values

Growing a diet deficient in certain elements by hydroponics, J F McCILNDON and WM C POSTER (by invitation) *Hahnemann Medical College, Phila* Elements unessential for plants may be eliminated from animals' diet by growing plants in solutions free from them. A tank of 2 x 12 ft surface, holding 200 liters requires at least twice during summer 60 grams potassium phosphate, 100 calcium nitrate, 125 potassium nitrate, 50 magnesium sulfate and 25 ammonium sulfate, dissolved separately. When fluorine (for instance) is to be eliminated, 95% of the potassium phosphate is mixed with 5% of the calcium nitrate (and the potassium nitrate) causing a precipitate of apatite. The remainders of the potassium phosphate and calcium nitrate are mixed to form a second precipitate. The first mixture is filtered into 2.5 cc concentrated sulfuric acid and the second mixture poured on the same filter, followed by the magnesium and ammonium sulfates. The filtrate is diluted to 200 liters with deionized rain water and the pH adjusted to 4.5 (with thymol green) in the tank. To this is added 1 cc of 30% ferrous sulfate daily. Manganese and boron should be added but zinc and copper may already be present. Corn, soy beans, sunflowers, alfalfa, clover and rice were grown in tanks covered with aluminum foil and aerated through porous carbon tubes. Sodium glutamate is added to diets deficient in chloride and sodium chloride to those deficient in other halogens. Potassium chloride is added to diets deficient in sodium.

Studies of L casei factor ("folic acid") in macrocytic anemias CARL V MOORE, OLGA S BIERBAUM (by invitation), Robert W Heine (by invitation) and ARNOLD D WELCH *Schools of Medicine of Washington Univ, St Louis, and Western Reserve Univ, Cleveland, and their Associated Hospitals* Spies, et al and Moore, et al have reported that synthetic *L casei* factor produces dramatic remissions in pernicious and other macrocytic anemias. Our findings indicate that either oral or parenteral administration is effective and that incubation with gastric juice does not render oral doses (10 mgm) more effective. Despite the similarity of the clinical response to that induced by liver, the synthetic factor appears to have less activity, on a weight basis, than that reported for certain liver fractions. Incomplete studies of the minimal effective parenteral dosage suggest that 5 mgm or more daily are required to induce a maximal hemopoietic response. In one patient, rectal administration (100 mgm daily) produced a nearly maximal effect, subsequent oral administration of the same dose produced a secondary response.

One subject, with findings characteristic of pernicious anemia, showed only slight reticulocyte responses during successive 10 day periods of daily injections of 1, 6 and 12 mgm, respectively. The erythrocyte count and hemoglobin level have increased slightly, in keeping with the small reticulocyte responses. Additional tests are now in progress, prior to determining the response to liver extract.

A study of the possible occurrence of relapses, despite the continued administration of the synthetic factor, is in progress.

The gastric intrinsic factor of Castle does not appear to be concerned directly with the release of free folic acid from its naturally occurring conjugated forms, the amount of *L casei* factor in yeast extract was not increased by incubation with neutralized normal human gastric juice.

Carbohydrate metabolism of riboflavin-deficient dogs AGNES FAY MORGAN, MARY GOODY (by invitation) and HELEN E AXELROD (by invitation) *Lab of Home Economics, Univ of California, Berkeley* (Read by title) Ten young dogs of three litters were fed from weaning a purified diet of 45.8 or 18 per cent casein content with adequate vitamin supplements or lacking only riboflavin. Four of these animals were given all the vitamins and six were deprived of riboflavin. Blood analyses were made at regular intervals and glycogen determinations on sacrifice. The growth of the two deficient dogs given the lower protein diet was markedly impaired as compared with the four on the high-protein diet. Acute deficiency symptoms occurred after 184 and 188 days in the former and after 196 to 307 days in the latter. The drop in hemoglobin was more marked in the high-protein group and was followed by dehydration possibly due to pylorospasm in the terminal stage. The glucose tolerance of the deficient dogs was much reduced. The deficient animals suffered coma and hypoglycemic convulsions with extremely low blood sugars in the final stages. The livers were found to contain 15 to 24 per cent fat and practically no glycogen. The heart and muscles had normal glycogen content. The adrenals were without exception severely hemorrhagic and the spleens were much reduced in size. [Supported by a grant from The Nutrition Foundation, Inc.]

Further studies on the availability to human subjects of thiamine from yeasts HELEN T NESS (by invitation), FUNG H FUNG (by invitation) and HELEN T PARSONS *Dept of Home Economics, Univ of Wisconsin, Madison* Feeding certain viable compressed bakers' yeasts to human subjects in this laboratory has sharply reduced urinary thiamine and lowered body stores, presumably by removal of thiamine from ingested foods and failure to release it for absorption.

Compressed yeasts with concentrations of "self-contained" thiamine (i.e. absorbed or synthesized

from nutrient media during propagation) of 5, 10 and 25 μg per gram¹ failed to release thiamine and reduced that absorbable from the food. Yeasts of higher content comparable to the following series are being tested.

This series of yeasts had, besides "self contained" thiamine, varying additions of thiamine by mechanical mixture after propagation, totaling 25 to 250 μg per gram¹ in a range of from equal proportions of the two types of thiamine to ten times as much thiamine added mechanically as was "self contained." Urinary thiamine remained uniform or fell only slightly on supplements of the less fortified yeasts, but rose significantly on the more highly fortified.

In general there seems to be a trend for mechanically fortified yeasts to yield thiamine more thoroughly the greater the fortification, although availability did not show complete correlation with thiamine concentrations. The general trend, if confirmed, may indicate that added thiamine is mainly adsorbed outside the cell, or is held more loosely in the cell protoplasm, it has been established that retention is not a function of the degree of phosphorylation.

Gradations of injury to the cell by heating or drying resulted in increased availability of thiamine, roughly correlated with the degree of loss of viability from injury or with ease of release of thiamine *in vitro* into the supernatant.

Riboflavin excretions and test dose returns of young women during periods of positive and negative nitrogen balances. HELEN OLDHAM (by invitation), ELIZABETH LOUNDS (by invitation) and THELMA PORTER, Dept of Home Economics, Univ of Chicago, Chicago, Ill. Three young women were maintained on weighed diets for three periods of ten days each. Daily nitrogen intakes were low (approximately 5 grams) in period I, high (19 grams) in period II and low (5 grams) in period III, while daily riboflavin intakes were kept relatively constant at 1.0 to 1.4 mg. Urinary riboflavin and nitrogen excretions were determined daily, the amounts in food and feces on individual 5 day composites. Daily nitrogen balances were calculated by subtracting daily urinary excretions and average daily fecal excretions from average daily intakes.

Daily urinary excretions of riboflavin varied inversely with the nitrogen intakes, averaging 372, 124 and 255 γ respectively on nitrogen intakes of 5, 19 and 5 grams. This occurred even though the riboflavin intake was higher during the period of high nitrogen intake.

The majority of the nitrogen balances were negative (av., -1.1 gram) on the 5 gram intake and all were positive (av., +5.4 grams) on the 19 gram intake. Daily urinary riboflavin excretions averaged 407 γ during the days when the subjects

were in negative balance (1.0 gram or more) and 123 γ during those when they were in positive balance (1.0 gram or more).

This suggests that riboflavin and reserve protein are closely connected, that riboflavin is released when reserve protein is depleted and stored with it when it is replenished.

Riboflavin test dose returns, measured before the study began and at the end of each period, increased progressively on these intakes. The possible significance of this will be discussed.

Dietary protein and porphyrin metabolism in the rat JAMES M. ORTEN and JUDITH MACKEY KELLER (by invitation), Dept of Physiological Chemistry, Wayne Univ. College of Medicine, Detroit. A study was made to determine the effect of a synthetic diet low in protein (3.5 per cent casein) but adequate in all other respects on the fecal excretion of protoporphyrin in the rat. Control rats were fed the same diet but with the level of casein increased to 22.5 per cent.

The porphyrin content of the feces was quantitatively determined by a modification of Watson's method for protoporphyrin in erythrocytes. Hemoglobin determinations were made by an acid-hematin method at regular intervals during the 16 week period of observation.

The porphyrin excretion of the low protein rats was consistently less than that of the control animals when calculated either as micrograms of protoporphyrin per day or per 100 grams of body weight, but the excretion was somewhat greater when expressed as micrograms per gram of dietary protein ingested. The porphyrin excretion of the low-protein rats decreased progressively during the experiment while the usual chronic anemia developed.

If protoporphyrin excretion is an index of porphyrin synthesis, these data indicate that dietary protein serves as a precursor of the porphyrin nucleus in the rat and that porphyrin formation, like hemoglobin formation, has a high "priority rating" for available protein in the organism.

The pantothenic acid content of tissues of the hen as influenced by diet. P. B. PEARSON and V. H. MELASS (by invitation), Texas Agricultural Experiment Station, College Station. Mature hens were fed diets containing 385 μg and 1575 μg of pantothenic acid per 100 grams of feed. After a period of not less than one year on the experimental diets, samples of blood were taken from individual hens and pantothenic acid assays made on the whole blood, plasma and cells. The average values expressed in micrograms per 100 ml are given below.

Pantothenic acid in diet	Blood	Plasma	Cells
1575 μg / 100 grams	43.6	51.6	21.9
385 μg / 100 grams	20.0	20.9	13.0

¹ On moist basis

From these data it is apparent that the level of pantothenic acid in the whole blood, plasma and cells of the chicken is definitely influenced by the amount in the diet. On an adequate level of pantothenic acid in the diet the amount in the blood and plasma is more than double that for hens on a low intake of 385 μg per 100 grams of feed. The percentage of cells in the blood was not affected by the level of pantothenic acid in the diet.

Hens on the two levels of pantothenic acid were killed and pantothenic acid assays made on the liver, leg muscle (gastrocnemius) and breast tissue. The amount of pantothenic acid in the tissues was definitely influenced by the amount ingested by the hen. The amount of pantothenic acid in the tissues of the hen fed an adequate level is significantly higher than in corresponding tissues of herbivorous animals.

Availability to human subjects of riboflavin from yeasts. ECHO L. PRICE (by invitation), MONA M. MARQUETTE (by invitation) and HELEN T. PARSONS, *Dept. of Home Economics, Univ. of Wisconsin, Madison* (Read by title). In tests paralleling thiamine studies, four samples of viable, compressed yeast containing circa 15 μg of riboflavin per gram of moist yeast failed to release this vitamin for absorption, this agreed with the results on thiamine. However, unlike the immobilization of thiamine of the food mixtures by these live yeasts, the utilization of riboflavin was not interfered with, since urinary outputs of the human subjects were uniform during the basal and yeast-supplemented periods.

When the viability of these four yeast samples was destroyed by brief heat treatment prior to ingestion, the riboflavin was available to the human digestive tract for absorption as the thiamine had been. Apparently the tenacity of the living yeast cell to withhold these vitamins from absorption was abolished by destroying the viability of the yeast cell.

Feeding a type of viable, compressed, fortified yeast in which only one-tenth of the riboflavin present in the sample was produced by the cell during propagation, showed that the riboflavin was so largely available for absorption that destruction of the viability of the cells yielded no measurable increase in the availability of riboflavin.

The difference in susceptibility to interference of the absorption of riboflavin and thiamine in the presence of live yeast cells is in accord with their fate in the brewing of beer. Practically all of the riboflavin except that synthesized by the yeast is found in the wort, whereas large amounts of thiamine pass into the yeast cells from the wort leaving little in the beer.

Metabolism of ascorbic acid by guinea pigs. MARY E. REID (introduced by Helen T. Parsons)

Division of Physiology, National Inst. of Health, Bethesda 14, Md. Three week old guinea pigs of an inbred strain were placed in metabolism cages and fed a pelleted diet lacking ascorbic acid but otherwise presumably complete. Five milligrams of ascorbic acid per 100 grams of body weight were injected daily. The urine was collected in metaphosphoric acid. Determinations of the amount of ascorbic acid excreted were made daily by the indophenol titration method and once per week by the osazone method of Roe and Kuether.

There was little difference in the excretion values obtained by the two methods. The output per 100 grams of body weight increased from an average value of 0.59 mg. for the 4 to 8 weeks age period to 1.05 mg. in the almost full-sized animals 6 months old. With each break in the growth curve there tended to be an increase in the amount of the vitamin excreted.

Preliminary tests have also been conducted to determine if the vitamin is used up in adult animals during wound healing. Skin wounds 10 cm. long were made down the center of the backs of 8 animals, the cut edges being fastened together with skin clips. Daily determinations were made of the ascorbic acid excreted during (1) the 10 days previous to wounding, (2) the 10 days of wound healing, and (3) the 10 days following wound healing. The results showed a 15% depression in excretion by the indophenol method and 22% by the osazone method during the second period. Values for the third period were approximately the same as for the first period.

Diet of mother and hydrocephalus in infant rats. L. R. RICHARDSON and A. G. HOGAN, *Dept. of Agricultural Chemistry, Univ. of Missouri, Columbia*. The 230 female rats in Group 1 received Diet I, composed of casein 30, cerelese 52, wood pulp 3, lard 10, and salts 5. Each 100 grams of the ration contained 3000 I.U. of vitamin A, 425 I.U. of vitamin D, 2.5 mg. each of alpha-tocopherol and of 2-methyl-1, 4-naphthoquinone, 1 mg. each of thiamine, riboflavin, and pyridoxine, 4 mg. of calcium pantothenate, 5 mg. of nicotinic acid, 100 mg. each of choline, inositol, and p-aminobenzoic acid, and 20 mcg. of biotin. The 54 females in Group 2 received Diet II, a mixture of Diet I and an eluate of a fuller's earth adsorbate of a liver extract. A total of 1756 young in Group 1 survived at the weaning age of 28 days and in addition there were 30 which developed hydrocephalus, between the ages of 10 and 24 days. Of these 30 only 2 survived as long as 28 days. A total of 1020 young in Group 2 survived until they were weaned and several thousand young were reared in the stock colony, with no indication of hydrocephalus. The data indicate that the abnormality is due to a deficiency of an unidentified nutrient, which is present in the liver eluate and in many natural

foodstuffs. It is suggested that hydrocephalus in other animals, including man, may be due to an inadequate diet.

Nutrition survey in Puerto Rico UNA L. ROBINSON¹ and RAMÓN M. SUÑERZ (introduced by Marianne Goettsch) *Nutrition Research Laby, Dept of Medicine, School of Tropical Medicine, San Juan, Puerto Rico*. One hundred and ten subjects were studied. Nutritive values for 86 weighed diets were calculated. Determinations were made for hemoglobin and red blood cells, plasma vitamin A, carotene and ascorbic acid, urinary thiamine, riboflavin and F₂ factor. Stools were examined for intestinal parasites. Physical examinations were made for clinical evidences of malnutrition.

Using 70 per cent of the National Research Council's recommended allowances as a minimum for adequate nutrition, the following percentages of the population were below the recommendation for each nutrient: calories 87, protein 94, calcium 95, iron 65, vitamin A 95, thiamine 87, riboflavin 97, niacin 55 and ascorbic acid 73.

Blood and urine analyses showed that the following percentages of the people had critically low levels for the various constituents: 31 for hemoglobin, 31 for red blood cells, 82 for vitamin A, 84 for carotene, 63 for ascorbic acid, 37 for thiamine, 83 for riboflavin and 78 for F₂ factor. Forty three per cent had hookworm, although its presence did not necessarily coincide with low hemoglobin.

There was some correlation between physical findings and dietary and biochemical evidences. By Baldwin-Wood and Life Insurance tables, 31 per cent were 10 to 30 per cent underweight, abnormal tongues were found in 35 per cent, conjunctival changes, including Bitot's spots in 98 per cent, hyperkeratosis and other skin manifestations in 60 per cent, active or healed cheilitis in 15 per cent, bleeding and/or spongy gums in 77 per cent.

Utilization of thiamine and riboflavin by lactating women CHARLOTTE RODERUCK (by invitation), HAROLD H. WILLIAMS and ICIE G. MACY *Research Laby, Children's Fund of Michigan*. Healthy multipara who had successfully nursed their children cooperated in the study of thiamine and riboflavin utilization during their first ten days postpartum and five day studies during the period of mature milk production. Five day composites of the food "as eaten," twenty-four hour collections of breast milk expressed manually, and 24-hour urine samples were analyzed.

Calorie and riboflavin intakes approximated the Recommended Allowances for lactating women, but thiamine intakes were 35 to 45% lower. However, the status of all subjects with respect

to thiamine and riboflavin was satisfactory, as was indicated by the 24 hour urine excretions and by hourly excretions in fasting samples.

Eighteen per cent of the thiamine consumed appeared in the milk and urine during the first five days postpartum, 23% during the second five days and 30% during mature milk production. In the same periods, riboflavin output was 49, 88 and 52% of the intake.

Supplementation of the diet with thiamine, raising the intake from 1.3 mg to 13 mg per day, increased the concentration of thiamine in the milk 62% and the excretion in the urine thirteen times. Combined, the percentage in milk and urine was similar before and after supplementation, 30 and 34%, respectively. Increasing riboflavin intake about five times caused parallel increases in the riboflavin in the milk, but larger increases in the amounts in the urine raised the total output from 52 to 74% of the intake.

Vitamin B₆ bioassay P. S. SARMA (introduced by C. A. Elvehjem) *Dept of Biochemistry, Univ of Wisconsin, Madison*. The bioassay for vitamin B₆ using the rat as the experimental animal measures the total activity of the vitamin in any natural material and may be due to pyridoxine, pyridoxamine, pyridoxal and possibly other related compounds. The methods employed to date have not been entirely satisfactory since the basal diets have contained crude preparations of liver concentrates, which contributed a small but variable amount of vitamin B₆. The diet has now been simplified to a considerable extent by the addition of some of the newer vitamins in pure form and consists of sucrose 75%, fibrin 18%, salts IV 4%, corn oil 3% together with all the vitamins except vitamin B₆ supplied in adequate amounts. Fibrin was chosen instead of casein as the source of protein since it was found that the growth on the deficient diet containing the latter was influenced by the presence of biotin and inositol. For assay purposes, weanling rats were depleted for two weeks on the deficient diet and then placed on diets containing known amounts of vitamin B₆ and the materials to be investigated. Values obtained by this method check well with those obtained by the yeast—*Saccharomyces carlsbergensis* method in the case of many foods but the values obtained for yeast and liver extract are higher by the rat assay than by the yeast assay.

The substitution of dextrin for sucrose in the basal ration was found to cause a marked growth increase in rats kept on the deficient diet. Results obtained from xanthurenic acid excretion studies and from the growth of rats on dextrin rations containing lard or sulphathiazole indicate that vitamin B₆ is produced in the intestinal tract and utilized by the rat.

The effects of copper on liver tumor induction

¹ On leave from Indiana University

by p-dimethylaminoazobenzene GIORGE R SHARPLESS *Dept of Labys, Henry Ford Hospital, Detroit* In a study of trace elements which may influence the formation of liver tumors in rats fed p-dimethylaminoazobenzene (butter-yellow), it has been observed that an increase in dietary copper can prolong the induction period of the tumors

Copper sulfate was fed in three concentrations, 0.15, 0.3 and 0.5% of the diet. This will provide an approximate minimum copper intake of from 1.8 to 6.2 mg per rat per day. The highest concentration was toxic when fed in a purified diet containing 10% casein but in a diet containing 4% casein and 5% dried brewers yeast the animals lived as long as littermate controls without copper. The riboflavin content was maintained at 0.2 mg per hundred grams of diet in order to favor tumor formation.

Copper did not prevent the development of tumors but the induction time, determined by either palpation or the period necessary for the tumor to kill the animal, was increased from 25 to 50%. During the induction period and also after large tumors had formed there was much less non-malignant liver damage in the copper fed rats.

While it has been reported that copper in large doses can be a factor in the development of liver cirrhosis, in these studies with butter-yellow it provided considerable protection against liver damage.

Vitamin B complex studies with diets differing in the carbohydrate component HELEN R SKEGGS and LEMUEL D WRIGHT (introduced by Richard H Barnes) *Nutritional Labys, Dept of Pharmacology, Medical Research Division, Sharp and Dohme, Inc, Glenolden, Pa.* An investigation of the effect of the type of dietary carbohydrate as related to the administration of succinylsulfathiazole has been made since it has been shown that dietary carbohydrate is a factor in the production of certain B complex deficiencies. Rats received purified diets containing sucrose, cereose, lactose, dextrin or corn starch as the dietary carbohydrate with and without the coadministration of succinylsulfathiazole. Studies were made of the fecal elimination and hepatic storage of folic acid, riboflavin, nicotinic acid, pantothenic acid and biotin, and the bacterial flora of the feces. At intervals food intakes were recorded and white blood cell and differential counts taken.

The diets containing lactose failed to promote growth or survival. With the remaining diets, irrespective of the type of carbohydrate, the inclusion of succinylsulfathiazole resulted in a combined folic acid and biotin deficiency characterized by leucopenia, agranulocytosis, alopecia and diminished fecal elimination and hepatic storage of folic acid and biotin. From the be-

ginning of the experiment, the ingestion of the sulfonamide markedly reduced the fecal elimination of folic acid. The fecal elimination of riboflavin, nicotinic acid, pantothenic acid and biotin was not directly depressed by the sulfonamide. When the succinylsulfathiazole fed rats had developed signs of deficiency and had shown loss of appetite, the elimination of riboflavin, nicotinic acid, pantothenic acid and biotin fell below that of the control animals. With the exception of a diminished *E. coli* count in animals receiving succinylsulfathiazole, the fecal flora was not altered demonstrably by the type of dietary carbohydrate.

Further studies on dogs with the progressive paralysis which responds to biotin SUSAN GOWER SMITH *Dept of Medicine, Duke Univ School of Medicine, Durham, N. C.* Dogs suffering from progressive paralysis produced on a basic diet free from the B complex but supplemented by eight synthetic B factors have continued to respond specifically to relatively small therapeutic doses of biotin (average 1 milligram total dose). Twelve such responses have been observed. In ten of these the reversal of the process was complete, in two, it was only partial due to death by cardiac failure. Two attempts to maintain dogs in which the process had been completely reversed by biotin resulted in freedom from typical neurological symptoms for a period of thirteen days (from attack to attack). It is obvious then that something else in addition to biotin is concerned in the etiology of the syndrome.

We suspected a mineral defect. The mineral salt mixture is extremely low in potassium and the syndrome appears somewhat similar to familial periodic paralysis in man. There is some evidence that calcium is of positive therapeutic value and that the magnesium metabolism is disturbed. Since it is not clear as yet the exact part played by potassium, calcium and magnesium, further studies are being made to determine their relationship to each other and to biotin.

Note Slides and a movie demonstrating dogs in the prodromal and progressive stages of paralysis have been made and can be shown if time permits.

Nitrogen metabolism as influenced by level of caloric intake, character of diet, and nutritional state of animal GLADYS STEVENSON (by invitation), PEARL P SWANSON, WANDA WILLMAN (by invitation) and MIRIAM BRUSH (by invitation) *The Nutrition Lab, The Foods and Nutrition Section, Iowa Agricultural Experiment Station, Ames*. A marked depression in the quantity of nitrogen present in urines of adult rats reduced to a constant plane of metabolism by feeding a nitrogen-low ration (20 per cent fat) has been observed when eggs are incorporated in the basal diet at a level equivalent to 3.5 per cent protein. There is

approximately 100 mg less nitrogen in urines collected in the second 7-day period than in the first. Interestingly, a daily dose of 30 mg of *dl* methionine is as effective as 400 mg of nitrogen derived from egg proteins. When protein supplements such as pork muscle, casein, gelatin, rat muscle or liver are fed, an increase in nitrogen excretion occurs.

Upon systematic reduction of the energy value of the diet, the sparing action of egg proteins is lost when calories are cut to less than 50 per cent of normal intake. In contrast, the effect of methionine is maintained when the diet contains only 25 per cent of the needed calories.

When rats are fed a basal diet low in fat, depression in urinary nitrogen occurs when caloric needs are fully or three fourths satisfied. Reduction of calories to 25 per cent of the requirement accelerates destruction of body tissue to a point equivalent to that observed in complete starvation. If rats are given the basal high-fat diet supplemented with methionine immediately after withdrawal of a full adequate ration, an even more dramatic and disastrous effect upon nitrogen metabolism is observed with restriction of calories.

Nutritional improvement of cereal flours and cereal grains I Influence on growth and efficiency of protein utilization of additions of small amounts of dried cultured yeast (strain G)¹ to the proteins in enriched white flour and table corn meal BARNETT SURE *Dept of Agricultural Chemistry, Univ of Arkansas, Fayetteville*. The yeast served as a source of protein enrichment. Growth experiments were carried out on albino rats for ten week periods. Biological values were calculated as gains in weight per gram of protein intake. The rations were supplemented with an abundance of the vitamin B complex and fat soluble vitamins.

Enriched Flour, was fed at 84 per cent plane of intake. There were six males and six females in each of the enriched wheat flour and table corn meal experiments. Replacement of 1, 3, and 5 per cent enriched flour by equivalent amounts of yeast in rations resulted in increase in body weight, percentagely, of 122.3, 180.5, and 226.5, and increases in biological value of 56.6, 82.2, and 96.3 per cent, respectively.

Table Corn Meal, was fed at 89 per cent plane of intake. Replacement of 1, 3, and 5 per cent table corn meal by equivalent amounts of yeast in rations resulted in increased growth, percentagely, of 85.0, 236.6, and 305.5, and increased biological value, percentagely, of 35.0, 96.2, and 95.0, respectively.

Since the diets of people of low income levels are derived largely from cereal grains, great benefits from additions of dried cultured yeasts in every day cookery, as protein supplements as

well as excellent sources of the vitamin B complex, may be readily anticipated.

Nutritional improvement of cereal flours and cereal grains II Influence on growth and protein utilization of additions of small amounts of dried brewers' yeast (strain K)¹ or soybean flour to the proteins in enriched white flour BARNETT SURE *Dept of Agricultural Chemistry, Univ of Arkansas, Fayetteville* (Read by title). Growth experiments were conducted with albino rats for a period of 10 weeks in this study as well as in those reported in the succeeding abstracts in this series. Also, in this and the following reports biological values were calculated as gains in weight per gram of protein intake. The rations in this and the subsequent studies were fortified with an abundance of all the known vitamins. There were 12 to 18 animals in each experiment.

The enriched white flour was fed at a 84 per cent plane of intake. Replacement of 1, 3, and 5 per cent enriched white flour with equivalent amounts of brewers' yeast (K) in rations resulted in increased gain in body weight, percentagely, of 71.3, 131.0, and 150.5, and in increases in biological values of 35.2, 54.5, and 55.7 per cent, respectively. Substitution of 1, 3, and 5 per cent enriched white flour by equivalent amounts of solvent extracted soybean flour produced increased gains in body weight, percentagely, of 55.2, 103.3, and 192.4, and increases in biological values of 23.9, 48.8, and 60.2 per cent, respectively. When 5 per cent enriched flour was replaced by 4 per cent soybean flour and 1 per cent of brewers' yeast, the increase in biological value was 71.6 per cent, in other words, the yeast produced a supplementary effect of 11.4 per cent.

Nutritional improvement of cereal flours and cereal grains III Influence on growth and protein utilization of additions of small amounts of soybean flour to the proteins in corn meal BARNETT SURE *Dept of Agricultural Chemistry, Univ of Arkansas, Fayetteville* (Read by title). The milled corn meal, sold on the market as "table corn meal" was used in this study and was fed at an 89 per cent plane of intake. There were 6 male and 6 female rats in each experiment.

Substitution of 1, 3, and 5 per cent of the corn meal by equivalent amounts of solvent-extracted soybean flour in the rations resulted in increased body weights, percentagely, of 86.0, 172.4, and 270.7, and increase in biological values of 46.8, 70.9, and 96.0 per cent, respectively.

Nutritional improvement of cereal flours and cereal grains IV Influence on growth and protein utilization of additions of small amounts of soybean flour to the proteins in polished rice BARNETT SURE *Dept of Agricultural Chemistry, Univ of*

¹Anheuser Busch, St. Louis Mo

¹Anheuser Busch, St. Louis Mo

Arkansas, Fayetteville (Read by title) The polished rice was fed at an 89 per cent plane of intake. There were 9 male and 3 female rats in each experiment. 2-date data is available on 8 weeks growth experiments, the results of which are as follows:

Replacement of 1, 3, and 5 per cent polished rice in the rations by equivalent amounts of solvent-extracted soybean flour resulted in increased growth, percentagely, of 22.2, 90.2, and 133.8, and increase in biological values of 4.5, 28.1, and 28.1 per cent, respectively.

Nutritional improvement of cereal flours and cereal grains V Influence on growth and protein utilization of additions of small amounts of dried cultured yeast (strain G)¹ to the proteins in polished rice BARNETT SURE *Dept of Agricultural Chemistry, Univ of Arkansas, Fayetteville* (Read by title) The polished rice was fed at an 89 per cent plane of intake. There were 9 male and 9 female rats in each experiment. The experimental period was 10 weeks.

Replacement of 1, 3, and 5 per cent of polished rice in rations with equivalent amounts of dried cultured yeast (strain G)¹ resulted in increased growth, percentagely, of 41.3, 59.1, and 69.0, and increase in biological values of 15.7, 15.7, and 10.7 per cent, respectively.

Nutritional improvement of cereal flours and cereal grains VI Influence on growth, reproduction, lactation and protein utilization of additions of increasing amounts of soybean flour to the proteins in enriched white flour in presence of 5 per cent dried skimmed milk powder BARNETT SURE *Dept of Agricultural Chemistry, Univ of Arkansas, Fayetteville* (Read by title) The enriched white flour was fed at an 80 per cent plane of intake. There were 1 male and 5 female rats in each experiment. The reproduction periods were 150 to 160 days. Replacement of 5, 7.5 and 10 per cent enriched flour with equivalent amounts of solvent-extracted soybean flour resulted in increased body weight, percentagely, of 74.3, 86.5, and 106.8, and increased biological values of 25.3, 29.8, and 15.8 per cent, respectively. Reproduction was successful in all groups of experiments but lactation was most successful in the group which received 10 per cent soybean flour. There was abnormal lactation in the control group receiving no soybean flour, the lactation period lasted 42 days compared with a lactation period of 23 and 21 days in the groups receiving 5 and 10 per cent soybean flour in the ration, respectively.

Nutritional improvement of cereal flours and cereal grains VII Influence on growth and protein utilization of additions of small amounts of soybean

flour or dried cultured yeast (strain G)¹ to the proteins in enriched flour in the presence of 6 per cent dried skimmed milk powder BARNETT SURE *Dept of Agricultural Chemistry, Univ of Arkansas, Fayetteville* (Read by title) The enriched flour was fed at an 83 per cent plane of intake. There were 3 males and 3 females in each experiment.

Replacement of enriched flour with 3 and 5 per cent solvent extracted soybean flour resulted in increase in body weight, percentagely, of 41.2 and 47.9, and increase in biological value of 13.5 and 17.9 per cent, respectively. Substitutions of 3 and 5 per cent enriched flour with equivalent amounts dried cultured yeast (strain G)¹ produced increases in body weight, percentagely, 43.6 and 43.1, and increases in biological value of 17.3 and 21.1 per cent, respectively.

Corneal vascularization as a sign of dietary deficiency in the rat V. P. SYDORSTICKER, W. K. HALL (by invitation), C. W. HOCK (by invitation) and A. P. BRIGGS (by invitation) *Depts of Medicine and Biochemistry, Univ of Georgia School of Medicine, Augusta*. It has been observed that the rat is prone to develop vascularization of the cornea as a result of deficient diets. This lesion has been described in rats deprived of vitamin A, riboflavin, tryptophan and lysine.

We have investigated the effects of deficiencies of various vitamins of the B complex, of deprivation of methionine, of protein-free and fat free diets and of total starvation.

In our experiments deficiency of thiamine and of niacin produced no ocular changes visible with the slit lamp. Deficiency of pyridoxine and of pantothenic acid produced mild grades of corneal thickening and opacity with subsequent vascularization of the cornea.

A diet lacking in methionine caused corneal opacity and vascularization in about 50 per cent of the experimental animals.

A diet exceedingly low in protein caused the death of young rats before any ocular changes occurred. Older rats developed marked thickening and opacity of the cornea followed by extensive vascularization.

A fat-free diet produced xerophthalmia and dense corneal vascularization similar in all respects to the changes which occur in vitamin A deficiency. It seems certain that this effect was due to deficiency of vitamin A, the result of failure of absorption of the carotene supplied in the absence of fat. The livers of animals in this experiment showed very low content of vitamin A.

Starvation resulted in death of rats of all ages before any ocular changes were apparent.

In all experiments in which corneal changes

¹ Anheuser-Busch, St. Louis, Mo.

¹ Anheuser-Busch, St. Louis, Mo.

were produced by deficient diets, cure was effected by supplying adequate amounts of the lacking nutrient

The provitamin A requirement of laying hens M WIGHT TAYLOR and WALTER C RUSSELL *Dept of Agricultural Biochemistry, New Jersey Agricultural Experiment Station, Rutgers Univ, New Brunswick* The provitamin A requirements of laying hens has been determined using a practical mash and grain ration in which alfalfa meal and yellow corn were the only sources of the factor Carotene and cryptoxanthin were determined periodically by chromatographic separation on activated calcium phosphate in order to control the provitamin A feeding levels

A level of 1650 International Units per pound of feed gave entirely satisfactory responses, equal to those obtained when 3000 units per pound was fed At a feeding level of 1100 units per pound, egg production showed a significant drop during the last 4 months of a 9 5 month feeding period but hatchability trials, carried on from the third to the fifth months, gave normal results and there was no significant increase in mortality When 525 units of vitamin A was furnished per pound of feed, vitamin A deficiencies appeared after 3 5 months and at the end of 6 5 months, 82 per cent of these birds were dead The concentration of vitamin A was determined in the blood plasma and found to be roughly proportional to the feeding levels but probably primarily dependent on body storage of the factor The minimum provitamin A requirement of the laying hen is placed at approximately 1400 International Units per pound of total feed No significant difference was observed in the requirements for high egg production and for good hatchability

Realimentation gain of rats on protein-fat diets as affected by various liver supplements HARRY M VARS and JULIUS SCHULTZ (by invitation) *Harrison Dept of Surgical Research, Univ of Pennsylvania, School of Medicine, Philadelphia* Using the Addis technique (*J Biol Chem*, 116 343, 1936) of starvation followed by ad libitum feeding for one week, the increase in body weight and liver protein has been determined in adult rats The control diet furnished 50 per cent of the total calories as protein (casein) and an equal amount as fat In addition all rats received supplements of thiamin, riboflavin, Ca-pantothenate, pyridoxine, nicotinic acid, inositol, choline chloride and p-aminobenzoic acid Experimental diets contained whole liver or extracted liver cake (to replace part of the casein), or various fractions of a variety of liver extracts

The greater realimentation gain in body weight and liver protein afforded by diets containing certain liver products was due to the presence of another factor or factors not included in the supplements mentioned above Removal of pyridoxine

from the supplements decreased the gains Nucleic acids as such were not the realimentation stimulants (*J Exp Med*, 67 467, 1939, *Am J Physiol*, 129 685, 1940) The addition of crystalline B₆ (Pflüger) increased the realimentation gain over the controls, though it may not replace the whole activity of various liver extracts

This method of study appears to offer a relatively quick method for assaying the biological activity of these accessory food factors

Reproduction and lactation in mice on synthetic diets Nutritional effects of choline EDWARD A WHITE (by invitation) and LEOPOLD R CERECEDO *Dept of Biochemistry, Fordham Univ, New York City* (Read by title) This investigation was undertaken to study the choline requirement of the albino mouse for reproduction and lactation Two basal diets were used One (diet A) consisted of purified casein (Smaco), 25%, sucrose 53, Crisco 10, lard 5, salts 5, and Ruffex 2 The following supplements were added per kilo of diet thiamine 10 mg, riboflavin 10 mg, pyridoxine 10 mg, calcium pantothenate 100 mg, vitamin D 5000 I U, alpha tocopherol 40 mg, and beta carotene 2 mg The animals were placed on this ration at weaning On this diet 23% of the litters were weaned Better results were obtained when diet A was supplemented with choline (1 5 gram per kilo of diet) On such a ration, 36% of the litters were weaned This diet could be further improved by a supplement of a crude folic acid concentrate (one norite adsorption and elution, 1 5 gram per kilo of diet) Fifty per cent of the litters were weaned

The other basal diet used (diet B) was the same as diet A except that the casein content was increased to 33% at the expense of sucrose No beneficial effect on lactation of the higher content of protein as compared with diet A was observed There was a distinct improvement noted when diet B was supplemented with choline (55% of the litters weaned) Further improvement of the diet was obtained on addition of the folic acid concentrate (65% of the litters weaned) [Aided by a grant from the John and Mary R Markle Foundation]

Some relationships between the nutritive properties and the streptogenin contents of proteins D W WOOLLEY *The Rockefeller Inst for Medical Research, New York* Streptogenin is a peptide-like bacterial growth factor (or factors) which occurs most abundantly in tryptic digests of some highly purified proteins Its possible relationship to the nutrition of animals has been suggested by the following facts The rate of growth of mice to which nitrogen was supplied only as an adequate mixture of amino acids was submaximal and was increased by additions of small amounts of certain

proteins. A number of proteins have been assayed for this growth-promoting property for mice and microbiologically for their strepogenin contents. Crystalline trypsinogen and casein were most potent and egg white, horse hemoglobin and gelatin were almost inactive. A rough quantitative relationship existed between strepogenin content and potency for the animals. During chemical fractionation of casein digests strepogenin was concentrated to about the same extent as was the

growth promoter for mice. The relationship between strepogenin content and growth-promoting action for mice was also demonstrated with a ration prepared from intact protein rather than amino acids, this ration contained 18 per cent egg white, a protein low in strepogenin but otherwise nutritionally adequate. These facts suggest, but do not prove, that strepogenin content is correlated with that nutritional property of proteins not represented by known amino acids.

THE AMERICAN ASSOCIATION OF IMMUNOLOGISTS

THIRTIETH ANNUAL MEETING

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(For possible corrections in any of the following abstracts see the next issue)

Pamaquine naphthoate as a prophylactic for malarial infections. HARRY A. FELDMAN, HENRY PACKER (by invitation), FRANKLIN D. MURPHY (by invitation), ROBERT BRIGGS WATSON (by invitation). *Dept. of Preventive Medicine, Univ. of Tennessee College of Medicine, Memphis, and the Health and Safety Dept., Tennessee Valley Authority (RBW)*. In 1931 James demonstrated that pamaquine in doses of 80 milligrams on the day before, the day of sporozoite inoculation, and on each of the six following days protected volunteers against both *Plasmodium vivax* and *Plasmodium falciparum* (Rumanian strains) infections. Smaller doses of the drug failed to exert this effect. The work reported in this paper is, apparently, the only repetition and extension of James' studies.

Pamaquine naphthoate (approximately 45 per cent base) was administered in varying dosage and for varying periods of time to thirty-six subjects who were infected with either *P. vivax* (McCoy) or *P. falciparum* (Costa) sporozoites. Both 180 and 160 milligrams on the day before, the day of, and for five or six days following inoculation have postponed or prevented infection for ten months.

In the case of *P. falciparum*, the post-inoculation period of treatment could be shortened to three days and still obtain complete protection for a similar period of time.

Smaller doses or shorter periods of drug exhibition uniformly resulted in failures.

Methemoglobinemia was regularly encountered. Two cases of acute hemolytic anemia occurred among the 11 negro patients. One of these re-

ceived a second course of pamaquine with similar effect.

Abdominal pain severe enough to force withdrawal of the drug occurred in one white male.

Elevations of the serum bilirubin and moderate hematocrit decreases were commonly encountered among those receiving the higher, more prolonged courses.

Except for the fact that the drug appears to affect the "tissue" but not the sporozoite forms of the parasites, the mode of action of pamaquine as a prophylactic (or suppressive) for malaria was not elucidated. [The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Univ. of Tennessee.]

Distribution of carbonic anhydrase in the pallium of Rhesus monkey and man as compared with that of lower mammals. WINIFRED ASHBY and J. SCHILLER. *Blackburn Lab., Saint Elizabeth's Hospital, Washington*. A further study of the quantitative distribution of carbonic anhydrase in the pallium was made. The method used by Keilin and Mann was employed at $3^{\circ}\text{C} \pm 0.1$.

Previous study had shown in man a greater amount of carbonic anhydrase in the white matter immediately below the cortex than in the cortex while the reverse situation of a greater amount of the enzyme in the cortex had been found in the dog, the hog and the cat. The present study extended the investigation to four Rhesus monkeys in the brains of which, the same proportioning of enzyme content as was found in man, occurred.

In the brain of a horse on the other hand, the

relationship found was the same as that of the dog, the hog and the cat

The possibility was considered that potassium, present in large amount in the erythrocytes of man and known to stimulate brain metabolism, might play an auxiliary role to carbonic anhydrase in the more vascular cortex and be a factor in causing the primate pattern. This was ruled out by the fact that both the horse and the hog, two of the animals giving the pattern of distribution of the lower mammals, have a high potassium content in their erythrocytes

It is postulated that this greater content of enzyme beneath the cortex found in the primates may be part of a phylogenetic pattern leading to the greater capacity for association believed to be the distinguishing quality of the mentality of man

The characters of the rabbit papilloma virus. JOSEPH W BEARD The virus responsible for endemic infectious papillomatosis in cottontail rabbits and capable of inducing in domestic rabbits warty growths which frequently become cancerous has been purified by ultracentrifugation and its characters examined by chemical and physical methods. From elementary and component chemical analysis, the virus is essentially nucleoprotein and the nucleic acid has been isolated and identified. Studies were made on sedimentation properties in the ultracentrifuge and electrical behavior in the Tiselius apparatus. The rate of diffusion of the virus and the viscosity of virus preparations were determined. The size and shape of the virus have been investigated in conventional electron micrographs and in micrographs of particles "shadowed" with gold. The density and water content of the virus in aqueous suspension were determined by centrifugation in bovine serum albumin solution and calculations made of the diameter of the wet virus. The findings are discussed in relation to their implications with respect to the status of the agent

Effect of antigen-antibody union in the circulating blood in production of anaphylactic reactions in passively sensitized mice KENNETH L BURDON *Dept of Bacteriology and Immunology, Baylor Univ College of Medicine, Houston, Texas* Mice passively sensitized by the intravenous or intraperitoneal injection of anti horse or anti-eggwhite serum show slight or no illness when the shocking dose of antigen is given by either route after the usual "incubation period" of 24-48 hours. Likewise only minimal reactions result when antigen (or antiserum) is injected intravenously or intraperitoneally immediately after intraperitoneal inoculation of the antiserum (or antigen). But when both antiserum and antigen are injected intravenously, one right after the other, severe or fatal anaphylactic shock is usually produced, the effect is the same whichever substance is injected

first. The material first inoculated is demonstrable in the circulating blood at the time reactions occur, but not later (after 24 hours) when inoculation of the second reagent usually causes no symptoms. Suitably proportioned antigen-antiserum mixtures injected intravenously induce similar severe illness. The reactions are specific and truly anaphylactic in nature, as shown by many control experiments. Recovered animals are refractory when tested by re-injection of both antiserum and antigen almost simultaneously, as in the original tests. These findings add to evidence refuting familiar tenets of the cellular theory. They show that the so called incubation period is not an essential feature of passive anaphylaxis and that the fixation of antibody upon the body-cells is not necessary for production of anaphylactic reactions. In mice severe anaphylactic symptoms evidently result from antigen antibody combination in the circulating blood. Incidentally the experiments demonstrate that the anti anaphylactic state is not due to lack of reacting antibody

Allergenic and anaphylactogenic properties of vaccines prepared from embryonic tissues of developing chicks II **Anaphylactogenic properties of typhus fever vaccines and equine encephalomyelitis vaccine** E J COULSON and HENRY STEVENS These investigations evaluate anaphylactogenic properties of egg yolk sac vaccines and chick embryo vaccines. Yolk sac vaccines were represented by several experimental and commercial lots of typhus vaccines. One lot of encephalomyelitis vaccine represented chick-embryo vaccines

Anaphylactogenic properties were investigated by gross anaphylaxis in guinea-pigs. Sensitizing capacities were estimated from the minimum dose of vaccine which, when administered to normal guinea-pigs, sensitized the animals to the degree that fatal anaphylaxis was induced by subsequent intravenous injection of the same vaccine or egg white. The relationship of antigens present in the yolk sac vaccines to antigens of corresponding extracts of normal chick embryo yolk sac and to antigens of fresh egg were investigated by the Schultz-Dale method

In contrast to previously reported studies on yolk sac vaccines the typhus vaccines examined were active anaphylactogenic agents, their potency in this respect was of the same order as egg white when compared on the basis of protein nitrogen. Antibodies in the uterine muscles of guinea pigs sensitized with yolk sac vaccines were identified chiefly with antigens of fresh egg. No evidence of anaphylactic sensitivity to embryonic proteins or to the anti-typhus immunizing factor was observed in animals sensitized with typhus vaccine

To the extent that antigenic activity in guinea-pigs provides a basis for estimating the likelihood

of unfavorable reactions during routine immunization of an unselected population against typhus fever with these vaccines, our results signify a possible risk to potentially allergic individuals and a definite danger to individuals who are allergic to egg proteins [Contributed from Allergen Investigations, Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U S Dept of Agriculture]

Serum albumin as a protective rather than nutritive growth factor in bacteriological media. BERNARD D DAVIS¹ and RAY J DUNN. *The Rockefeller Inst for Medical Research, New York 21, N Y* The addition of a water soluble ester of oleic or stearic acid ("Tween") to a liquid medium has been shown to permit submerged and more rapid growth of tubercle bacilli, but this medium fails to support the growth of very small inocula of a human strain. Addition of 0.1% bovine or human serum albumin makes such growth possible. A number of other proteins (gelatin, casein, gliadin, egg albumin, lactalbumin, serum globulin, pressed yeast juice) fail to exert this beneficial effect. The mode of action of the albumin does not appear to be nutritive since 1) it depends on the essential integrity of the protein, trypsin-digested or heat-coagulated albumin being without effect, 2) although the growth-promoting factor is non-dialyzable, a solution of albumin suspended in the medium in a cellophane bag promotes growth. Since there is no contact between the protein and the bacteria, it is clear that the albumin must exert its effect by interaction with dialyzable constituents of the medium.

Albumin antagonizes the inhibitory effect of various toxic substances added to bacteriological media (fatty acids, heavy metals, antiseptics) and is known to form complexes with many compounds. In the present medium the chief role of albumin appears to be that of binding traces of free fatty acid released from the Tween.

All growth factors are therefore not necessarily true nutrients, in the sense of being assimilated by the organism, but may also promote growth by binding traces of inhibitory compounds. This property of serum albumin suggests its possible value in eliminating interference by contaminating substances in microbiological assays.

The comparative susceptibility of various laboratory animals to *B. tularensis*. CORA M DOWNS, LEWIS L CORIELL, GIFFORD B PINCHOT, EDWARD MAUMENEE, ALICE KLAUBER, S S CHAPMAN and BARBARA OWEN. The ability of *B. tularensis* to infect man and some of the lower animals by way of various portals of entry is well known. In order to determine as accurately as possible the

numbers of *B. tularensis* necessary to infect commonly used laboratory animals by various routes, the study reported here was undertaken. The organisms used were fully virulent strains of *B. tularensis*. The standard bacterial suspension consisted of a 24 hour dextrose, cysteine, blood agar culture suspended in saline or saline gelatine to give 40% light transmission in a Coleman spectro photometer and contained 1 to 2 billion organisms per ml as determined by mouse titration and plate count. A summary of the results shows that the LD₅₀ dose as figured by the Reed and Muench method was 1 ml of 10⁻³ dilution of a standard suspension when administered intracutaneously and subcutaneously in mice, rabbits and guinea pigs. The intraperitoneal dose was also 1 ml of 10⁻⁴ dilution in mice and guinea pigs and 1 ml of 10⁻¹ dilution in rats. The percutaneous dose was much more variable: 10^{-4.5} in mice, 10⁻¹ in rats, 10^{-2.5} in rabbits and 10^{-1.5} in guinea pigs. The intranasal dose was 10^{-6.5} in mice, 10^{-2.5} in rats and 10⁻⁷ in guinea pigs. The conjunctival and intravaginal dose for rabbits was 10⁻⁶.

In addition to the above results the LD₅₀ dose by subcutaneous administration was determined for hamsters and cotton rats to be 10⁻³ and 10⁻⁴ respectively. Although the exact LD₅₀ dose by the various routes was not determined for chicks, dogs and monkeys, the following data is presented to show the variation in susceptibility exhibited by these animals.

One chick infected with 100 million organisms died and two which had received 10 million and 100,000 respectively became infected and when sacrificed 17 days later yielded positive cultures. In the case of three other chicks, one injected with 10 million organisms died and the ones receiving 100 million and 100,000 survived and showed no evidence of infection when sacrificed.

Eight pups and one adult dog became infected when they were given doses similar to those given the chicks, but only 4 out of the 9 died.

It was not practicable to determine the LD₅₀ dose by various routes in monkeys but avirulence titration showed that these animals are quite susceptible, succumbing to as few as 20 organisms given subcutaneously.

Summary. The results on these various routes of infection of animals showed that *B. tularensis* was infective by all routes tested and in general the animals were most susceptible when challenged subcutaneously or intraperitoneally. The susceptibility of the animals varied with the species, the dog, chicken and white rat being most resistant, the mouse, hamster, guinea pig and rabbit being least resistant in the order named and the cotton rat and monkey having somewhat greater resistance than the rabbit but less than the white rat. Action of chemotherapeutic agents on the or-

¹ Sen Asst Surgeon, Tuberculosis Control Division, U S Public Health Service

ganism of granuloma inguinale WOLCOTT B DUNHAM and GEOFFREY RAKE *Division of Microbiology, The Squibb Inst for Medical Research, New Brunswick, N J* The chemotherapeutic activity of various compounds was tested by injecting mixtures of the drugs and suspensions of *Donovania granulomatis* into embryonated eggs Experiments were also performed to compare the *in vivo* with the *in vitro* activity of streptomycin

Mercurous chloride and antimony potassium tartrate were more effective than the bismuth and arsenic compounds tested Sulfonamides were relatively ineffective Streptomycin and streptomycin were more active than penicillin

Immunization against malaria In experimental animals JAMES FREUND, K J THOMSON and H E SOMMER *Public Health Research Inst of the City of New York and the Dept of Health, Bureau of Labys of the City of New York* Rhesus monkeys injected twice with formalin killed *P. knowlesi* emulsified in paraffin oil containing killed tubercle bacilli survived with parasitemia of low grade when infected with 1000 or more *P. knowlesi* Control animals receiving the same infecting dose died or were killed with high parasitemia Injection of formalin killed parasites without these adjuvants failed to protect

Ducks receiving formalin killed *P. loophuræ* in saline solution or in water in oil emulsion containing killed tubercle bacilli were protected against subsequent infection with *P. loophuræ* as compared with controls The protection lasted longer with adjuvants

In unprotected monkeys and ducks there was a rapid decrease of circulating red blood cells coincident with the development of parasitemia In protected monkeys and ducks in spite of the low parasitemia, the red blood cell count decreased in similar fashion These observations suggest that removal of parasitized cells from the circulation may play a part in protection

Differences in the avidities of tetanal toxins for nerve tissue U FRIEDENMANN, A HOLLANDER and F B TRAUB *Dept of Bacteriology, The Jewish Hospital of Brooklyn* Qualitative differences between tetanal toxins were uncovered by the method of the indirect test In this test serial dilutions of antitoxin were injected intravenously while 20 lethal doses of the individual toxins were given intracerebrally or intramuscularly The minimal protecting doses of antitoxin (A_1) in the intracerebral as well as in the intramuscular test were very different for the individual toxins When toxin and antitoxin were mixed *in vitro* the antitoxin requirements were approximately the same for all toxins With the aid of special methods it could be shown that the differences in the A_1 values of the individual toxins are due to differences in their avidities for nerve tissue Under

conditions as they prevail in the natural disease toxins with high avidities for nerve tissue are practically resistant to antitoxin

Cytotoxic property of mouse cancer antiserum ROBERT G GREEN *Medical School, Univ of Minnesota, Minneapolis* Antiserums have been prepared in rabbits by the injection of centrifugates of mouse mammary cancer tissue collected between 14,000 \times gravity and 100,000 \times gravity The rabbits were bled for serum 14 days after the last of 5 weekly injections Such an antiserum neutralizes the milk agent of Bittner In testing for its cytotoxic property, suspensions of cancer cells were mixed with the antisera and after 3 to 6 hours were injected into susceptible hybrid mice No tumors developed Cancer cell suspensions in 0.9% saline solution uniformly produced tumors upon injection An antiserum prepared from rabbits immunized with centrifugates of lactating glands of susceptible but non-infected mice did not appreciably lower tumor production below the controls nor did normal rabbit serum The antibodies of the cancer antiserum were completely removed by absorption with a suspension of mouse cancer cells but were not removed by a suspension of cells similarly prepared from lactating normal mammary glands The antigenic character of the mouse cancer cell appears to be different from that of the normal mouse cell and similar to that of virus centrifugates prepared from mouse cancer tissue

The bactericidal action of streptomycin DOROTHY HAMRE, GEOFFREY RAKE and RICHARD DONOVICK *Division of Microbiology, The Squibb Inst for Medical Research, New Brunswick, N J* *In vitro* studies showed that streptomycin has bactericidal action on both young growing cultures and on resting cells of susceptible organisms This is in contrast with the action of penicillin where organisms in the resting stage are unaffected

Studies also were made of the streptomycin resistance of bacterial cells which survive given concentrations of streptomycin

The fate of injected particulate antigens in relation to the formation of antibodies T N HARRIS and W E EHRLICH *The Children's Hospital of Philadelphia, the Philadelphia General Hospital and the Departments of Pediatrics and Pathology, School of Medicine, Univ of Pennsylvania* Earlier studies have shown that the injection of antigenic material into the pad of the rabbit's foot is followed by the appearance of antibodies in the regional lymph node, in lymph produced by that node and especially in lymphocytes in such efferent lymph In the present work the fate of particulate antigenic material has been investigated in the period between its injection into the foot of

the rabbit and the appearance of antibodies in the regional lymphatic tissue

It has been found that a soluble substance immunologically specific for the antigenic material injected can be identified in extracts of the injected tissue and of the regional lymph node, and in the efferent lymph from that node. The concentration of this soluble material falls off slowly in the injected tissue in the course of the few days following the injection. In the extract of the lymph node and in the lymph it falls off quickly, and is succeeded by the appearance of antibody.

Evidence is presented that this material is derived from the injected antigenic material by a physiologic process, and this process is discussed as the means by which antigens which are originally parts of cells are made available to the lymphocyte.

The role of selection in antigenic variation of blood parasites. JAMES A. HARRISON, *Dept of Biology, Temple Univ.* Extensive studies on antigenic variation in cultures of *Paramecium aurelia* are presented as evidence for the thesis that the appearance in experimental animals of successive relapse strains of trypanosomes having new anti-

gen characters is essentially due to a process of selection and is not the result of antibody action upon the individual parasites which grow into the relapse strains. In test-tube experiments, simulating as far as possible the situation involved in the development of antibody-fast strains of trypanosomes in the mouse, it has been shown that antibody-fast strains of paramecia are commonly developed when cultures are grown in antiserum to which they are sensitive. In other test-tube experiments of a sort which is seemingly impracticable or impossible with trypanosomes, it has been shown that antibody-fast cultures of paramecia exceedingly similar, if not identical, to those developed in antiserum may be developed from individuals selected at random from cultures which have never been exposed to antiserum. From these and other experiments it appears that all types of variation which occur among paramecia grown in antiserum are within the normal potentialities of the animal and occur spontaneously without regard to the presence or absence of antibody.

Viruses of infectious hepatitis and serum jaundice. W. P. HAVENS, JR. (introduced by J. R. Paul). *Neurotropic Virus Disease Commission, Army Epidemiological Board Section of Preventive Medicine, and the Yale Univ. School of Medicine.* Although the exact relationship between infectious hepatitis and homologous serum jaundice is not understood, experiments in their transmission to human volunteers reveal information about the properties of the causative viruses.

Both agents are filtrable, resistant to a tempera-

ture of 56°C for 30 minutes, both have been transmitted to human volunteers in serial passage, and both give rise to a clinical disease in man which resembles "catarrhal jaundice."

In contrast to these similarities are certain differences which involve route of inoculation, duration of incubation period, and period of "infectiousness," including the period when the virus of each disease is demonstrable in the blood stream. There is no evidence furthermore, in these experiments that heterologous immunity exists, although homologous immunity is demonstrable in infectious hepatitis.

Our strain of infectious hepatitis virus produces disease in human volunteers following parenteral inoculation or ingestion. The incubation period ranges from 15-31 days. The virus is demonstrable in both blood and stool during the acute phase but not in the incubation or convalescent period.

Our strain of homologous serum jaundice virus is infectious when inoculated parenterally with a longer incubation period, 56-134 days. It is recoverable from the blood of inoculated subjects 3 and 4 way through the long incubation period and during the acute phase of disease, but not 1 month after onset. Apparently it is not present in the stool of patients, nor is it infectious when ingested. Patients convalescent 6 months from infection with this strain are not immune to experimental infection with infectious hepatitis virus.

Antibody formation in the immunization of human beings. MICHAEL H. FIDELBERGER, *Professor of Biochemistry, College of Physicians and Surgeons, Columbia Univ., and Chemist to the Presbyterian Hospital in New York City.* Quantitative data will be given on the magnitude of, and variations in, the antibody response of human beings to single injections of 0.03 to 0.06 mg. of the specific polysaccharides of pneumococci. The persistence of the observed antibody levels will be discussed and comparison will be made with existing relative data on antibodies to other antigens in such instances as these may be recalculated to approximate absolute values.

The effect of ultraviolet irradiation on various properties of influenza virus. WERNER HENLE and GERTRUDE HENLE, *Dept of Pediatrics, School of Medicine, Univ of Pennsylvania and The Children's Hospital of Philadelphia.* The hemagglutinating property of influenza virus in dialyzed allantoic fluid remains stable for extended periods of irradiation (60 minutes). Thereafter, it disappears suddenly. In contrast, the infectivity decreases rapidly to a fraction of one per cent and the toxicity to 25-50 per cent upon very short irradiation (10-30 seconds). Longer irradiation (1-3 minutes), which renders the preparations non-infectious and non-toxic, leaves the interfering capacity practically intact. After further exposure

(15-60 minutes) interference is no longer demonstrable whereas hemagglutination is unaltered. The immunizing capacity decreases gradually but even after 90-120 minutes of irradiation, where the hemagglutination can no longer be demonstrated, the fluid is still able to induce some immunity in mice against influenza. Finally, the total complement fixing activity is only slightly decreased at the end of 2 hours of irradiation.

These data offer some insight into the mechanism of infection of host cells in that they indicate that at least 3 distinguishable processes may take place: (a) Attachment of the virus to the cell as illustrated by the hemagglutination phenomenon, this may occur even after the interference phenomenon has been destroyed; (b) A change in the metabolism of the host cell, as illustrated by the interference phenomenon, which can occur even with inactive virus; (c) Multiplication of active virus in the cell and subsequent spread to other susceptible cells, as illustrated by infectivity of the virus. The role of toxicity in the infection has not been elucidated.

The role of latent pneumotropic viruses in acute respiratory disease. FRANK L. HORSFALL, JR. Evidence of infection with latent pneumotropic viruses was obtained in each of nine species of mammals, including man. Some animal species, i.e. mice, hamsters and cotton rats, may harbor two or more latent viruses in their respiratory tracts. Each of the latent viruses known to occur in the respiratory tracts is capable of inducing manifest disease. Such infections may result in the development of pneumonia which is sometimes fatal. Animals which have recovered from infection are immune to reinfection with the latent virus responsible for their initial disease.

Various non-specific stimuli are capable of unbalancing the equilibrium between latent pneumotropic virus and animal host. Such stimuli are provided by commonly used and apparently innocuous laboratory procedures, e.g. the intranasal instillation of non-infective foreign materials. When the equilibrium between latent virus and animal host is upset, infection commonly develops. This may be either inapparent and demonstrable only as a result of the altered immunological status induced or manifest and readily discernible as acute respiratory disease. The frequency with which non-specific stimuli are capable of provoking infection with latent pneumotropic viruses is related to the season, during winter months the effect is much more commonly elicited than in the summer.

Immunochemical studies on blood group A substance from hog stomach. ELVIN A. KABAT, AARON BENDICH (by invitation) and ADA E. BEZER (by invitation). *Dept. of Neurology, College of Physicians and Surgeons, Columbia Univ. and*

the Neurological Inst., New York. Immunochemical investigations on the blood group A substance from individual hog stomach linings have shown that active substances can not be obtained from all hogs. Stomach linings were subjected to peptic digestion and the digests purified by the Morgan and King phenol method. Of ten stomachs studied, seven yielded active products. Substances from the remaining three were obtained by this procedure in similar yield, which, except for their non-antigenicity in man and their immunological inactivity, had the same analytical properties as did the active ones. These inactive preparations failed to precipitate with human serum containing anti-A and did not inhibit the hemagglutination of A cells by anti-A. No significant chemical or physico-chemical differences between active and inactive materials have yet been found. Preparations obtained from pools of hog stomachs consist of a mixture of active and inactive substances which can not be separated by ordinary means. The immunochemical purity of such products can be estimated by determining the proportion of glucosamine carried down in specific precipitates formed in the region of antibody excess to the amount of glucosamine in the preparation added. Active preparations from individual hog stomachs approaching 100 per cent in purity, as judged by this criterion, have been obtained. [Work was done under contract with the Office of Scientific Research and Development.]

Hemoglobin precipitation with tissue extract antigen. REUBEN L. KAHN, ALBERT H. WHEELER, and ELIZABETH B. McDERMOTT. *Clinical Lab., Univ. Hosp., Univ. of Michigan, Ann Arbor, Michigan.* While investigating serum reactions in malaria, the question arose whether hemoglobin solution (laked erythrocytes) of malarial origin might differ serologically from hemoglobin solution of nonmalarial origin. It was observed that precipitation occurs on mixing hemoglobin solutions with tissue extract (Kahn) antigen. Hemoglobin solutions derived from malarial (vivax) erythrocytes were found to possess a greater tendency toward precipitation with the antigen than hemoglobin solutions derived from nonmalarial erythrocytes. Several factors affecting this precipitation phenomenon were investigated. These factors include: 1) The aging of the blood clots from which the hemoglobin is prepared; 2) The concentration of NaCl solutions used in the preparation of the hemoglobin solutions and of the antigen suspensions; 3) Solubility of precipitates in excess of lipid antigen or hemoglobin solution. Further studies of this precipitation phenomenon are in progress.

Studies of serum antifibrinolysin. MELVIN H. KAPLAN (introduced by John H. Dingle). *Respiratory Diseases Commission Lab., Regional Station Hospital, Section 2, Fort Bragg, N.C.* It has been

shown previously that the dissolution of plasma clots by streptococcal fibrinolysin is due to the proteolytic action of a plasma enzyme which is activated by fibrinolysin. The resistance of plasma clots to fibrinolysis observed under certain conditions in man and in various animal species results from factors in the plasma which interfere with any phase of this process. Such factors include the presence of antifibrinolysin, antiprotease, or the deficiency of an effective zymogen (lytic factor).

Antifibrinolysin specifically neutralizes fibrinolysin and is therefore an antibody to a kinase or enzyme-activator. Antifibrinolysin does not inhibit the enterokinase activation of trypsinogen. Consequently fibrinolysin and enterokinase are not identical although they are analogous in function. Quantitative studies indicate that antifibrinolysin combines specifically with fibrinolysin in varying multiple proportions. The reaction is approximately 90 per cent complete at the end of 30 minutes at 37°C, and equilibrium is reached within 60 minutes.

It was demonstrated by the use of a quantitative serological method of assay, which minimized non-specific antifibrinolytic effects, that no rises of antifibrinolysin occurred in 244 patients with non-streptococcal respiratory disease. The antifibrinolysin level of patients with streptococcal infections was quantitatively the same when measured with fibrinolysins from the three Lancefield groups of streptococci known to be fibrinolytic, A, C, and G. The increase in antifibrinolysin antibodies which developed as a result of infection by streptococci of groups A and C was quantitatively the same when tests were performed with heterologous fibrinolysins from group A, C, and G streptococci. It was concluded that antifibrinolysins produced by various groups of beta-hemolytic streptococci are immunologically identical.

Coexistence of two antibodies for crystalline insulin in human serum. MARY HEWITT LOVELESS, A diabetic woman, highly allergic to insulin, was "desensitized" cautiously during 3½ months. Controlled tests of the threshold type were performed on her skin, conjunctivae and serum before, during and after the experiment. Reagents (thermolabile, sensitizing antibodies) for insulin did not fluctuate importantly, as judged by passive-sensitization studies done with serum-dilutions. During treatment, the serum acquired thermostable antibodies adequate to neutralize 0.1 unit of crystalline insulin per ml, as revealed by testing serum-insulin mixtures in sensitized skin. The skin and conjunctivae now required decidedly more antigen before they showed visible reactions. When therapy was discontinued, these signs of immunity gradually disappeared. After two months, a previously tolerated dose of insulin gave rise to alarming urticaria, itching of the palms and loss of

consciousness without hypoglycemia. Clinical tolerance, circulating thermostable antibodies and heightened thresholds of reaction in the skin and eye were restored following a short "booster" course of crystalline insulin.

When the immune sera were added to lethal doses of crystalline insulin and injected into mice, it appeared that the patient's immunity against allergy was accompanied by a capacity to inactivate the hormonal function of insulin, for a majority of the mice survived. The serum from two insulin-resistant patients failed to protect mice. It is perhaps significant that 20 units of insulin failed to lower the fasting blood sugar of the allergic patient either during or between courses.

CONCLUSION. The clinical control of allergy for insulin rests on the development, during specific therapy, of thermostable antibodies similar to those found in treated hay fever patients. They appear to inactivate not only the allergenic but also the hormonal function of insulin. The mechanism in our cases of insulin-resistance without allergy seemed of a different nature.

The composition of specific precipitates from anti-tobacco-mosaic-sera. SAUL MALKIEL (introduced by W. M. Stanley), *Dept. of Animal and Plant Pathology, The Rockefeller Inst. for Medical Research, Princeton, New Jersey.* The quantitative behavior of viral-anti-viral systems has been but little investigated partly because of the lack of purified and chemically characterized antigens. Tobacco mosaic virus, which is available in a highly purified form, is an extremely strong antigen. The anti-sera prepared were of high titer for, at the point of optimal proportions, 0.007 cc of a given rabbit anti-serum was found to be equivalent to 1 mg tobacco mosaic virus when titrated by the method of Dean and Webb. The zone of optimal proportions did not coincide with the equivalence zone but was found to be in the region of excess antigen. Anti-sera in the horse and rabbit were prepared and these systems studied. The quantitative relationships of the specific precipitates were established by a determination of the antibody and antigen content. Since this antigen contains a known amount of phosphorous the antigen content was estimated by means of phosphorous determinations. Electron micrographs prepared by the gold plating technique of complexes of known antibody-antigen composition were presented. In general, for the system studied, viral complexes were similar to those of lower molecular weight soluble proteins.

The recovery of poliomyelitis virus from the stools of monkeys and chimpanzees experimentally infected by various routes. JOSEPH L. MELNICK (introduced by John R. Paul), *Section of Preventive Medicine, Yale Univ. School of Medicine.* Poliomyelitis virus introduced directly into the body of

monkeys by the intracutaneous route finds its way into the intestinal tract with some regularity. Virus introduced intraperitoneally and intracerebrally also may appear in the intestinal tract, but seems to do so less frequently. Thus the presence of the virus in the feces during the experimental disease does not indicate that the portal of entry was the mouth or upper nasal passages.

Excretion of virus in the experimental host is not peculiar to any one strain.

In some animals virus appeared in the stools before any symptoms of the disease in the central nervous system were apparent.

Following intracutaneous inoculation of virus in two chimpanzees, both animals became "healthy" carriers of the virus for two and four weeks respectively.

False positive reactions in serologic tests for syphilis. Nature and mechanism of selective inhibition by a heat-stable serum component. HANS NEURATH, ELLIOT VOLKIN (by invitation) and H. W. CRAIG (by invitation). *Depts. of Biochemistry and Bacteriology, Duke Univ. School of Medicine, Durham, N. C.* The serologic flocculation reaction of antibodies of biologic false positive human sera with lipoidal antigens is influenced by a component found in the crude "albumin" fraction of human sera (Science, 101 GS, (1945)). Addition of this component to serologically active globulin fractions prior to flocculation results in complete inhibition, whereas, addition subsequent to the formation of floccules causes complete redispersion of the latter. This effect is specifically directed toward false positive reactions, and under optimal conditions does not occur to a significant extent with antibodies from syphilitic human sera. The inhibitor is a heat stable lipo protein, probably associated with the alpha globulins.

Quantitative measurements of the influence of concentration of antigen, inhibitor and antibody demonstrate that in the region of antigen excess no inhibition occurs, while over a limited, intermediate range of antigen concentration the degree of inhibition is approximately proportional to the logarithm of inhibitor/antigen ratios. At constant optimal antigen and inhibitor concentrations, inhibition is largely independent of antibody titer. In regions of inhibitor excess, the reaction of syphilitic antibodies may also be progressively inhibited. The results are interpreted on the basis of a competition for the antigen between false positive antibody, inhibitor and syphilitic antibody, the relative affinities for the antigen increasing in the above order. [The work described in this paper was done under contract, recommended by the Committee on Medical Research between the Office of Scientific Research and Development and Duke Univ.]

The enhancement and properties of the comple-

ment-fixing antigens of lymphogranuloma venereum. CLARA NIGG, MAURICE R. HILLEMANN and BETTY M. BOWSER. *Virus Lab., E. R. Squibb & Sons, New Brunswick, N. J.* The activity of Lymphogranuloma venereum complement-fixing antigens prepared from infected yolk sac suspensions could be enhanced by treatment with phenol, boiling, or ether extraction.

Treatment with phenol in a final concentration of 0.5% at 4°, 37° or 56°C effected as much as sixteen fold enhancement. The rate of development of full potentiality at a given temperature depended on preliminary aging of the suspension.

Boiling such suspensions either before or after adding phenol effected the same degree of enhancement. Under certain conditions the relatively clear supernates of boiled phenolized antigens were as active as the whole boiled antigens. While phenolized antigens, boiled or unheated, frequently reacted nonspecifically with sera from early cases of syphilis, boiled supernate antigens were specific.

The complement fixing activity of unphenolized yolk sac suspensions could not only be quite completely extracted with ether, but eight fold enhancement could be demonstrated in such extracts. Preliminary aging of the suspensions for several weeks prior to extraction was important in obtaining full potential enhancement. The degree of dispersion of the extract in saline determined the degree of demonstrable enhancement. Ether extract antigens were never anticomplementary even though prepared from suspensions initially anticomplementary.

Unphenolized and phenolized antigens (unheated or boiled), phenolized boiled supernates, and ether extract antigens all retained group reactivity in that they reacted with sera of persons infected with other members of the Psittacosis-Lymphogranuloma venereum group.

Stability on boiling and autoclaving and ether solubility of the antigen suggest its glucolipid nature.

Coexistence of the antibodies of yellow fever and Weil's Disease in human serum. ARDROONY PACK-CHANIAN. *The School of Medicine, Univ. of Texas, Galveston.* Serum samples from a number of persons who had antibodies against yellow fever by attacks of sylvatic or jungle yellow fever were received from Brazil and tested for antibodies for Weil's Disease by microscopic agglutination tests against Type I, *Leptospira icterohaemorrhagiae*.

Out of 94 persons whose serum gave a positive mouse protection test for yellow fever, the serum of six had a diagnostic titre of the antibodies for Weil's Disease. The agglutination titre ranged from 1:100 to 1:1,000, the reaction was prompt and complete within two hours.

The presence of antibodies of both of these dis-

cases in a person made possible retrospective diagnosis and indicates that these six patients also contacted Weil's Disease either at the time of, before, or after the attacks of yellow fever

Penicillin sensitivity of staphylococcus *In vitro* tests R F PARKER *Dept of Medicine, Western Reserve Univ, Cleveland* The susceptibility of 150 strains of staphylococcus to the action of penicillin has been studied by means of a commonly employed test Serial two-fold dilutions of penicillin were prepared in nutrient broth, and inoculated with an over night culture of staphylococcus In parallel tests of each strain, 2 dilutions of culture were used, 10^{-2} and 10^{-6} After over-night incubation at 37°C the tubes were examined for the presence or absence of visible growth The lowest concentration of penicillin capable of preventing the appearance of visible growth was recorded as the inhibiting concentration

Using the test with the smaller inoculum as the index, it was found that 80% of the strains were inhibited by 0.06 units or less, and over 90% by 0.48 units or less of penicillin, resistance being more or less normally distributed The results of the 2 tests (with small and large inocula) were the same, or differed by only 1 tube, in about $\frac{3}{4}$ In about $\frac{1}{4}$ however, the difference was 6 tubes or more

It does not yet appear whether this sharp difference in the response to penicillin which depends upon size of inoculum is due to a difference in the reaction of the organisms to the substance, or to the greater frequency of occurrence of resistant mutants in some strains In using a test of this sort, however, it is obviously important to control the size of the inoculum if comparable results are to be obtained

Allergenic and anaphylactogenic properties of vaccines prepared from embryonic tissues of developing chicks I SKIN sensitivity following the subcutaneous inoculation of typhus vaccines in humans COLONEL HARRY PLOTZ *Division of Virus and Rickettsial Diseases, Army Medical School, Army Medical Center, Washington 12, D C, and the United States of America Typhus Commission, War Dept, Washington 25, D C* Virus and rickettsial vaccines prepared from cultures grown in chick embryo tissues are being used with increasing frequency The yellow fever and equine encephalomyelitis vaccines are prepared from chick embryos, the typhus and spotted fever vaccines from yolk sacs while the influenza vaccine is made from the allantoic fluid The following studies were undertaken to obtain information on the possible allergenic and anaphylactogenic properties of typhus vaccines

Only one of 180 normal adults, skin tested with typhus vaccines, egg white or egg yolk, showed evidence of skin sensitivity to the three antigens

This individual when subsequently inoculated subcutaneously with typhus vaccine developed no systemic reaction Of 150 adults receiving three subcutaneous doses of typhus vaccine, four developed skin sensitivity to the whole typhus vaccine alone, four to both egg yolk and typhus vaccine, one to both egg yolk and egg white, and one to egg yolk, egg white and typhus vaccine None of these subjects developed a general reaction when subsequently inoculated with typhus vaccine In spite of the fact that many millions of soldiers have received egg embryo vaccines, the number of severe reactions reported have been minimal However, 17 severe reactions and three deaths have been recorded when vaccines were given to allergic or egg sensitive individuals One death followed the administration of Rocky Mountain spotted fever, typhus and influenza vaccines Because of this, caution should be observed in the administration of egg vaccines to allergic or egg sensitive individuals Concentrated washed typhus rickettsial suspensions, which are relatively free of egg antigens, can be used as vaccine in these cases

Inhibition of glucose utilization in mouse brain homogenates by some viruses E RACKER and I KRIMSKY (introduced by C M MacLeod) *Dept of Bacteriology, New York Univ College of Medicine, New York* It was previously reported (Racker and Kabat, *J Exp Med*, 76: 579, 1942) that anaerobic glycolysis is inhibited in minced brains of poliomyelitis-infected mice Minced brain preparations produced about 0.5 mg of lactic acid per 100 mg of wet weight of brain per hour It was then found (Racker and Krimsky, *J Biol Chem*, in press) that by omitting Na^+ , and inhibiting DPNase by nicotinamide, brain homogenates produced 7.5 mg lactic acid per 100 mg of wet weight per hour

Homogenates from mice infected with the Lansing strain of poliomyelitis showed an average inhibition of 16% in the glucose utilization as compared with normal brain (average of thirty six experiments) Similarly, mice infected with the FA strain of Theiler mouse poliomyelitis virus showed an inhibition of 31% (average of twenty-four experiments)

This inhibition was localized in the first two steps in glucose breakdown, namely the formation of glucose-6-phosphate and hexosediphosphate When the latter compound was used as substrate, no significant inhibition of its utilization was found in the infected mouse brain [Aided by a grant from The National Foundation for Infantile Paralysis, Inc.]

Addition of a purified preparation of the Lansing strain of poliomyelitis to normal homogenates produced a similar inhibition of glucose phosphorylation

To investigate the specificity of this inhibition, two non neurotropic viruses were tested, namely influenza A and tobacco mosaic virus.¹ The same inhibitory effect was observed with these viruses. Inhibition varies with time, temperature and pH and fluctuates with different individual mouse brains.

The activity of some antibiotics and sulfonamides *in vitro* and *in vivo* upon the agents of lymphogranuloma venereum and feline pneumonitis. GREGORY RAKE and DOROTHY HAMRF. *Division of Microbiology, The Squibb Inst for Medical Research, New Brunswick, N J*. *In vitro* only commercial penicillin at 100,000 u/ml had any marked virucidal effect upon the agent of feline pneumonitis. Streptomycin, sulfathiazole, sulfamerazine, sulfaguanidine, and p- amino benzoic acid *in vitro* and *in vivo* had no effect in the concentrations used. *In vivo*, penicillin in much lower concentrations prevented death of the embryos infected with feline pneumonitis. A study of the retardation of growth of the agent in the yolk sac by penicillin was made. The agent of lymphogranuloma venereum was more susceptible to the action of penicillin.

Carbonic anhydrase content in the brain of rats with thiouracil induced cretinism. J SCHILLER, SALLA CORN and WINIFRED ASHBY. *Blackburn Laby, Saint Elizabeth's Hospital, Washington*. New born rats were injected subcutaneously with 125 mg of thiouracil daily for 15 days starting the day after birth. The dosage was increased to 25 mg during the following 15 days after which the animals were sacrificed. Only litter mates served as controls.

The efficiency of the drug was indicated by the inhibition of body weight (50% less than the controls), the inhibition in weight of brain (25% less than the controls), increase in the weight of the thyroid gland (28.5% over controls) and behavior.

The carbonic anhydrase content of the whole emulsified brain in thiouracil injected rats averaged 20.78 units per gram of tissue as contrasted with the 29 units per gram of tissue averaged by the normal controls. The lowering of 40% in the enzyme content was almost reached at the age of 15 days as shown by another group of rats injected with thiouracil for two weeks only when, however, body and brain weight were only 10% lower than in controls, but the thyroid showed an increase of over 100%.

It is concluded that there is a striking parallelism between the inhibition of the thyroid gland functions and that of the normal production of the enzyme during the post-natal development of the rat.

Anaphylaxis XVI. Studies on passive sensitiza-

tion of the dog. NOBLE P. SHERWOOD, O. O. STOLAND, J. S. KIRK (by invitation) and D. J. TENENBERG (by invitation). *Depts of Bacteriology and Physiology, respectively, Univ of Kansas, Lawrence*. According to Dragstedt and others passive sensitization in dogs cannot be demonstrated immediately even with antibodies from the same species. This is contrary to the results reported by Richet in 1907. We have repeatedly demonstrated the immediate passive sensitization of dogs by the simultaneous injection of antibody and antigen into normal dogs. Following shock and the return of the blood pressure to normal, desensitization was demonstrated in each case. As a source of antibodies we employed whole blood, blood serum, and heparinized plasma from sensitized dogs. In our experiments 10.0 ml of heparinized plasma per kilo of body weight of the recipient was sufficient for immediate sensitization. In an attempt to determine the duration of passive sensitization in dogs we injected each of 9 dogs with doses of plasma which we demonstrated would cause passive sensitization and tested them after a latent period of 72 hours. Eight of the nine were negative. In a previous paper we reported that one of 4 dogs passively sensitized was negative after 48 hours. We are inclined to interpret this as indicating that most dogs passively sensitized with homologous blood lose their sensitivity for antigen rapidly. [This work was assisted in part by a grant from the Graduate Research Committee of the Univ of Kansas.]

Metabolic requirements of gram-negative bacilli determining resistance to penicillin. GREGORY SHWARTZMAN. *Division of Bacteriology, Laby of The Mount Sinai Hospital, New York, N Y*. Amino acids affected significantly the action of penicillin upon Gram negative bacilli. Dicarboxylmonooamino acids (i.e. aspartic, glutamic, hydroxyglutamic acids and asparagine), cystine and α amino acids with guanidine, glyoxaline and pyrrole nuclei, all possessing in common —NH grouping in the nucleus (i.e. arginine, histidine and hydroxyproline, respectively) were antagonistic to the action of penicillin. The anti-penicillin effect of these amino acids could be reversed by dimethionine, the reversal being facilitated by methionine sulfoxide and threonine following a reciprocal quantitative relationship. When substances of mixed amino acid composition (broth or casein hydrolysate) were used for cultivation, a mixture of methionine, methionine sulfoxide and threonine markedly enhanced the susceptibility of *Brucella*, *Eberthella*, *Escherichia*, *Salmonella* and *Shigella* to penicillin.

Modifications in resistance to penicillin could be induced in the absence of the drug by altering the metabolic requirements of *E. coli*. Following a number of serial passages in basal medium alone

¹ We wish to thank Dr W. M. Stanley for these two purified virus preparations.

and in basal medium supplemented by amino acids antagonistic to penicillin, variants were obtained which differed markedly in resistance to penicillin. The changes were in inverse relation to concentration of antagonistic amino acids in the media used for the passages. The variants obtained from passages in basal medium alone apparently acquired the ability to synthesize penicillin-antagonists. They possessed the highest resistance to penicillin. Variants from cultures supplemented by antagonistic amino acids lost at least in part the ability for synthesis. They showed the highest susceptibility to penicillin. Furthermore, a variant was obtained which failed to grow in basal medium alone. It grew well when the medium was supplemented by leucine, hydroxyglutamic or aspartic acid. In basal medium containing leucine the susceptibility of the variant to penicillin was 9-12 times greater than in basal medium containing a dicarboxyl-monoamino acid. It is suggestive that certain intermediate products of dicarboxyl-monoamino acids may be responsible for the antagonism.

The studies seem to indicate a relationship between the antibiotic activity of penicillin and the cellular metabolism of Gram-negative bacilli.

Chemotherapeutic effect of nitroakridin and rutenol in rickettsial infections in eggs and mice. J. E. SMADEL, J. C. SNYDER, H. L. HAMILTON, J. P. FOX and E. B. JACKSON. *Division of Virus and Rickettsial Diseases, Army Medical School, Washington, D. C., the USA Typhus Commission, and the International Health Division, Rockefeller Foundation.* Nitroakridin and Rutenol, a related drug, exert a beneficial chemotherapeutic effect in mice and embryonated eggs experimentally infected with the following rickettsial agents: the Wilmington strain of murine typhus, the Breinl strain of epidemic typhus, the Karp strain of tsutsugamushi disease, and a strain of Rocky Mountain spotted fever.

Studies on influenza virus and vaccines. W. M. STANLEY. *The Rockefeller Inst. for Medical Research, Princeton, N. J.* Fundamental studies on the biochemical, biophysical and immunochemical characterization of influenza virus have been made. Conditions for obtaining optimum amounts of virus in allantoic fluids have been determined and the accuracy of different methods of estimating virus concentration has been established. Different methods for the purification, concentration and inactivation of influenza virus have been evaluated with a view to the development of procedures for the large scale production of influenza vaccines. A centrifuge method, involving the use of the Sharples centrifuge, was found to be superior to other methods for the purification and concentration of influenza virus. The product obtained by means of the centrifuge method con-

sisted mainly of virus, whereas other methods yielded products consisting of about 20 per cent or less of virus and about 80 per cent or more of non-virus materials. The yield of virus and the maximum concentration of virus obtainable by the centrifuge method were considerably greater than those obtainable by other methods. A method for the large scale production of a centrifuge-type influenza vaccine has been developed and is now in use for the production of vaccine for civilian use.

Allergenic and anaphylactogenic properties of vaccines prepared from embryonic tissues of developing chicks. III. A study to determine whether chick yolk sac vaccines contained sufficient egg proteins to cause severe systemic reactions if given to egg-sensitive individuals. ARTHUR STULL. This investigation was undertaken to determine whether chick embryo vaccines contained sufficient unaltered egg protein to elicit systemic reactions in egg sensitive individuals. Included also is a study of the serum from a patient who exhibited a severe local reaction following the second injection of encephalomyelitis vaccine (EEV).

The relative antigenic activity of chick-embryo vaccines, purified rickettsial bodies, yolk sac extracts, and fresh egg proteins was determined by a dilution method, using the passive transfer technique. The antigenic specificities of these preparations were determined by quantitative cross neutralization of egg sensitive sera. These tests showed that the vaccines contained egg proteins in sufficient quantity and of such specificity that inoculation of egg sensitive individuals with these vaccines might induce dangerous reactions. An immunizing dose (1 ml.) of typhus vaccine contained about 2000 times more egg-white protein than is recommended for safe intracutaneous tests. The purified rickettsial bodies were essentially free of egg antigens.

Neutralization tests revealed variations in the specificity of antibodies in egg sensitive sera. Antibodies in one serum were specific chiefly for egg white—in another, for both egg white and egg yolk. In the mentioned case, in which sensitivity was induced by inoculation with EEV, antibodies were detected for yolk sac, egg yolk, and probably also for chick-embryo, but none was detected for egg white. This serum contained no demonstrable precipitin and did not transfer sensitivity to guinea-pigs. Subsequent to inoculation with EEV this patient has had gastrointestinal disturbances with severe diarrhea after eating chicken or egg.

Circulating antibodies and the resistance of ferrets to reinfection with influenza virus. JOHN Y. SUGG and THOMAS P. MAGILL, *Dept. of Bacteriology, Cornell Univ. Medical College, New York, N. Y.* Adequate information concerning a possible cellular factor in the resistance of ferrets to rein-

fection by influenza virus is not available in the literature. In order to gain information on that point a group of ferrets were infected with strains of either influenza "A" or "B" virus, which were known not to produce antibodies against each other. When retested one week later the animals were found to be immune to the virus used for the original infection but fully susceptible to reinfection with the antigenically distinct virus. If the mechanism is the same in the case of infection with these two viruses, then the results indicate that a cellular factor is not involved or is involved only to a limited extent.

Another group of ferrets were infected with a strain (CC) of influenza "A" virus and retested six weeks later with the same (CC) or with another (WS) influenza "A" virus. The ferrets that received the same strain (CC) showed no signs of infection. Those that received the other strain (WS) gave a pronounced febrile reaction, however, these animals had a low titer of antibodies against the WS strain and their fever was of shorter duration than was the case with control animals.

Data comparing the febrile reactions of all of the animals with their titers of circulating antibodies are presented in the paper.

The detoxification by acetylation of soluble antigens from *Shigella dysenteriae* and *E. typhosa*. HENRY P. TREFFERS, BENJAMIN A. RUBIN (by invitation), and CLAIRE ABRAMS BELL (by invitation). *Dept. of Immunology, Yale Univ. School of Medicine, New Haven, Conn.* The toxicity of available vaccines against bacillary dysentery constitutes a serious barrier toward their widespread use. This investigation has been concerned primarily with protection against the Shiga dysentery organism through a reduction of the toxicity: antigenicity ratios of the somatic polysaccharide or polysaccharide protein antigens following acetylation of the purified materials with acetic anhydride.

The LD₅₀ of the undetoxified antigens in mice is about 0.20 mg., with significant weight losses occurring with 0.05 mg. In contrast, no deaths were observed in a group of 48 mice given 3.0 mg. of various acetylated fractions. A 60 fold or greater reduction in toxicity is therefore obtained on acetylation, which is confirmed by temperature and WBC measurements in rabbits.

Of 44 mice immunized subcutaneously with the toxic, unacetylated antigen, 3 (7%) survived the challenge dose of Shiga organisms in mucin, of 93 animals immunized with the antigen acetylated four hours or less, 19 (20%) survived challenge, of 119 animals immunized with antigens acetylated for more than four hours, 39 (33%) survived challenge. The latter represents 3.3 times the standard deviation and is statistically significant. None of the acetylated antigens produced agglutinins for

Shiga, although these can readily be produced with the toxic antigen.

The polysaccharide protein complex of *E. typhosa* may be similarly detoxified by acetylation, and the fractions confer considerable protection against the typhoid organism. [This work was performed under contract OEMcmr 499 recommended by the Committee on Medical Research of the Office of Scientific Research and Development, and Yale Univ. Preliminary investigation was made under a similar contract with Harvard Univ. (OEMcmr-170).]

The behavior of endocellular proteolytic enzymes (cathepsins) in experimental tuberculosis. CHARLES WEISS¹ and NELLIE HALIDAY.² *Research Lab., Mount Zion Hospital, San Francisco*. In the rabbit the inherent (natural) capacity of the organs (lungs, kidneys, liver and spleen) to destroy virulent tubercle bacilli is correlated with the speed of hydrolysis of their endocellular enzymes (Cathepsin II). Immunization with non-virulent bacilli followed by infection with virulent organisms results in an increased capacity to destroy tubercle bacilli (Lurie) and a parallel acceleration of the speed of the tissue enzymes. Injection of non-virulent bacilli alone does not affect the rate of proteolysis just as it failed to increase phagocytosis of tubercle bacilli in Lurie's experiments.

These observations and those of Gerstl and co-workers for the first time permit correlation of organ and species susceptibility to infection with tubercle bacilli with endocellular enzyme activity.

Tuberculo carbohydrate, prepared by Heidelberger's method, exerts a selective inhibitory action on Cathepsin II derived from tuberculous tissue, but is inert in the presence of normal tissue proteinase. The phosphatide and protein (PPD) fractions of tubercle bacilli are also inhibitors, but are not selective. It is possible that these substances prevent softening of caseous tuberculous foci. It is known that in caseous foci tubercle bacilli tend to die, whereas in areas of softening (cavities) they survive and multiply. Since softened areas may rupture into adjacent blood vessels or bronchi and thus cause dissemination of the infection, it is important to investigate the enzyme anti-enzyme balance under these conditions. In preliminary experiments, biotin and others of the group of B vitamins (thiamine, riboflavin, calcium pantothenate, niacin and inositol) which accelerate growth, were found to have no influence on the speed of cathepsin, even though the latter participates in the synthesis of proteins and in growth processes.

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Effect of various routes of administration of penicillin upon experimental lobar pneumonia in rats
 CATHERINE E. WILSON (by invitation), ANNE F. BYRNE¹ (by invitation), CAROLYN W. HAMMOND² (by invitation) and ELI ANOR A. BIRSS *Bacteriology Section, Medical Division, Chemical Warfare Service, Edgewood Arsenal, Maryland* Lobar pneumonia was produced in rats by the intrabronchial intubation of mucin suspensions of type I pneumococci. The mortality in untreated animals infected in this way was 97%. At autopsy they showed consolidation of one or more lobes of the lungs. Penicillin was given in three ways, i.e., by injections, by inhalation of an aerosol and by gavage. Each animal received three treatments by one of these routes at 6, 12, and 24 hours after infection. Aerosolization was accomplished by exposing 8 rats at a time in a special apparatus, to mists of known concentrations. When 500 units of penicillin was administered by inhalation or by intramuscular injection the survival rates were 97 and 100%, respectively. Approximately the same survival rate was obtained when 5000 units were given orally by stomach tube. When the dose was decreased by half, the survival rates were 75% following inhalation, 46% after intramuscular injection of the same amount and 63% after intubation with 2500 units. Thus somewhat better results were obtained following inhalation than from intramuscular injections of the smaller doses of penicillin (250 units per dose) while with the larger doses (500 units per dose) there was no difference between the per cent survivals by these two routes of administration. About 10 times as much penicillin given by mouth resulted in survival per cents that were not significantly different from those obtained by inhalation or injection.

Data on blood concentrations of penicillin following these doses and routes of administration will be given

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A study of the competition of lecithin and antitoxin for *Cl. welchii* alpha toxin (lecithinase), using a new, manometric technique
 PAUL C. ZAMFONIA and FRITZ LUDMANN (introduced by J. Howard Mueller) A manometric method has been developed which tests for the presence and activity of the *Cl. welchii* alpha toxin, recently demonstrated to be a lecithinase. This enzyme hydrolyzes lecithin, liberating phosphorylcholine and a diglyceride. The phosphorylcholine displaces carbon dioxide from a bicarbonate buffered medium, making it possible to follow the reaction kinetics by measuring the carbon dioxide liberated in a Warburg vessel.

The activity of the enzyme appears to be restricted to lecithin, since cephalin (phosphatidylethanolamine), phosphatidylserine, sphingomyelin, and glycerophosphorylcholine are not attacked. Calcium, cobalt, zinc, manganese, and magnesium activate the enzyme while barium, iron, aluminum, cadmium, strontium, and copper are inhibitors.

This method has provided an interesting tool for studying the competition of two classes of substances (substrate and antitoxin) to combine with the enzyme-toxin, as indicated by the following experiments:

(1) If toxin and antitoxin are mixed for 30 seconds, and then lecithin is added, the lecithin is not split.

(2) If toxin and lecithin are mixed for 30 seconds, and then antitoxin is added, the reaction proceeds, but is slowly decelerated, as compared with the control rate.

(3) If toxin is added to a mixture of lecithin and antitoxin, the antitoxin cannot prevent the reaction from taking place at a reduced rate.

In summary, the attraction of lecithin (substrate) for toxin (enzyme) is sufficiently great so that antitoxin is unable to stop the reaction immediately, once it has started. The antitoxin in this situation slowly applies a brake on the speed of the enzymatic process.

INDEX OF SUBJECTS OF ABSTRACTS

This is a single entry index. The number in parenthesis after each entry refers to the society of origin (1) Physiology, (2) Biochemistry, (3) Pharmacology, (4) Pathology, (5) Nutrition, (6) Immunology

A

Acceleration and flicker fusion (1)	54
Acceleration and fluid loss from blood to tissue spaces (1)	17
Acceleration anoxia and tolerance to (1)	35
Acceleration, anti blackout suits and blood pressure (1)	115
Acceleration blood pressure during (1)	59
Acceleration effects protection by inhaled carbon dioxide (1)	107
Acceleration environmental temperature and tolerance to (1)	18
Acceleration food and fluid in tolerance to (1)	17
Acceleration glycemia and tolerance to (1)	17
Acceleration human tolerance to (1)	68
Acceleration protection by immersion in water (1)	18
Acceleration tolerance to (1)	40
Acceleration voluntary protective maneuvers (1)	115
Acceleratory forces and their amelioration (1)	10
Acetylation of amines by acetyl amino acids (2)	122
Acetylcholine electrical activity of (1)	5
Acetylcholine enzymatic synthesis of (1)	145
Acid base reactions of quinoline and acridine (2)	139
Acid effects of ammonium compounds (1)	10
Acridines body disposition of (3)	206
Adhesions intraperitoneal (4)	218
Adrenal a sodium retaining substance of (1)	42
Adrenal and phagocytosis in spleen (1)	34
Adrenal constituents of injury (2)	128
Adrenal extract and hexokinase reaction (2)	150
Adrenal function after ovariectomy (1)	97
Adrenal function and psychomotor performance (1)	48
Adrenal hormones liver glycogen and muscle work (1)	78
Adrenal in efficiency plasma venin substrate level in (1)	19
Adrenal preparations protection against toxic material (1)	63
Adrenalectomy and urinary non protein nitrogen (1)	50
Adrenalectomy calcium pantothenate and survival (1)	63
Adrenalectomy respiration of nerves and arteries after (1)	3
Adrenalin and depressant action of alcohol (3)	153
Adrenalin central action of in raising blood pressure (1)	61
Adrenergic potentiation by pyribenzamine (3)	216
Apo changes in kidney function (1)	94
Aldolase crystalline (2)	158
Alkaloids cinchona (3)	165, 168, 175, 170, 185, 206, 214
Alkaloids fumarate action of (3)	163
Alveolar air concentration a new method of representing (1)	26
Amino acid oxidase of proteus (2)	157
Amino acid utilization in hypoproteinemia and anemia (4)	226
Amino acids separation of with ion exchangers (2)	123
Amino acids sulfur in growth (2)	144
Analgesia with butanone (3)	201
Anaphylactic reactions in passively sensitized mice (6)	245
Anaphylaxis passive sensitization and (6)	253
Anemia hyperchromic (1)	22
Anesthesia with propyl methyl ether (3)	187
Anesthetics topical irritation of (3)	167
Anorexia dextroamphetamine and gastro-intestinal innervation (1)	42
Anoxia and capillary permeability (1)	44
Anoxia, intermittent and body weight (1)	101
Anti tobacco mosaic-virus specific precipitates from (6)	250
Antibiotics and sulfonamides activity of (6)	253
Antibodies and other globulins cellular sources of (4)	220
Antibodies and resistance to influenza (6)	254
Antibodies for crystalline insulin (6)	250
Antibodies formation of and particulate antigens (6)	247
Antibodies of yellow fever and Weil's disease (6)	251
Antibody formation in immunization (6)	248
Anticonvulsant action of drugs (1)	26
Anticonvulsant properties of diphenylhydantoin (3)	180
Anticonvulsant properties of tridione (3)	179
Antimalarial properties and toxicity of quinolones (1)	2
Antigen antibody reaction membrane hypothesis of (1)	20
Antigen antibody union in anaphylactic reactions (6)	245
Antigen, tissue extract and hemoglobin precipitation (6)	249
Antigenic fractions of proteus (2)	121
Antigenic variation of blood parasites (6)	248
Antigens complement fixing of lymphogranuloma (6)	251
Antigens detoxification of by acetylation (6)	255
Antimony distribution and excretion of (3)	178
Antispasmodic action of piperidines (3)	163
Antitoxin and lecithin competition for alpha toxin (6)	256
Appetite in protein-depleted rats amino acids and (4)	218
Arsenic detoxification with BAL (3)	175
Arsenous oxide pharmacology of (3)	162
Atabrine and ventricular fibrillation (3)	193

B

Bacteriological media serum albumin in (6)	246
Ballistocardiogram abnormal forms of (1)	100

Barbital anesthesia proteins and resistance to (1)	72
Barbital, pentobarbital susceptibility (1)	72
Barbiturate-isoniprocaine antagonism (3)	211
Barometric pressure low and altitude "bends" (1)	66
Barometric pressure, low, and physiology of rat (1)	9
Barometric pressure low, and respiratory efficiency (1)	39
Barometric pressure low, memory and (1)	52
Barometric pressure respiratory exchange and (1)	20
Barometric pressure urine and phosphorus excretion and (1)	21
Benadryl properties of (3)	190
Benzene poisoning and inhalation of methyl disulphide (1)	63
Benzene poisoning methionine in (1)	63
Biologically active principles isolation of (2)	138
Blood acid base balance in asphyxia (1)	37
Blood and brain injected fructose and glucose in (2)	141
Blood and urine, mannitol in (2)	130
Blood anemia cholesterol and splenectomy (2)	140
Blood anemia produced by paraphenylene-diamine (3)	173
Blood arterial and alveolar oxygen tensions (1)	64
Blood arterial oxygen and rapid altitude change (1)	74
Blood capillary walls electrosmotic transport through (1)	60
Blood circulating cell volume (1)	83
Blood circulatory effects of sympathectomy (1)	97
Blood coagulation and silicones (1)	52
Blood coagulation during digitalization (3)	198
Blood coagulation, thrombin inactivation by antithrombin (4)	219
Blood cocarboxylase insulin and (1)	28
Blood disappearance curve of T 1824 in (1)	73
Blood dye concentration curves of arterial (1)	41
Blood dyscrasias treatment of (5)	231
Blood effect of aminopropiophenone on (1)	3
Blood effects of bone marrow spleen immune serum on (3)	176
Blood erythrocytes respiration of (1)	34
Blood flow and heat exchange in hand (1)	29
Blood flow cutaneous in evaluating fitness (1)	53
Blood flow estimation with the Thermistor (1)	13
Blood flow in aorta axial stream of (1)	103
Blood flow in bronchial artery (1)	13
Blood flow in periphery intermittence of (1)	76
Blood gas tensions cerebral flow and oxygen consumption (1)	55
Blood hemoglobin activity of dried (2)	133
Blood hemoglobin intravenously (2)	136
Blood hemoglobin utilization when parenterally introduced (1)	73
Blood humoral factor in hemostasis (1)	117
Blood hypertension essential high spinal anesthesia in (1)	62
Blood hypertension renal and vitamin K (1)	75
Blood immune proteins of cow (2)	154
Blood lactic and pyruvic acid levels (2)	139
Blood macrocytic anemia and folic acid (5)	232
Blood maintenance of active hemoglobin (2)	132
Blood microcytic anemias folic acid and (5)	236
Blood O ₂ and CO ₂ dissociation curves of Atlantic Salmon (1)	8
Blood oxygen and pulmonary ventilation (1)	50
Blood oxygen in intravenous barbiturate anesthesia (1)	7
Blood oxygen saturation and morphine (2)	132
Blood pemphigus detoxification of (1)	69
Blood pressure and pulse rate related to body temperature (1)	44
Blood pressure effect of diethylstilbestrol on (1)	46
Blood pressure effective venous and pericardium (1)	10
Blood pressure indirect in rat (1)	98
Blood pressure injected local anesthetics and (3)	167
Blood pressure rise by oxygen lack and autonomic agents (1)	106
Blood protein fractionation after injury (2)	146
Blood prothrombin determination (2)	150
Blood recruitment from spleen during hemorrhage (1)	78
Blood red cell life and heme formation (2)	153
Blood red cells anaerobic glycolysis of (2)	131
Blood red cells ionic and osmotic equilibria of (1)	51
Blood reduction time of cutaneous (1)	84
Blood renal hypertension and hog renal extract (1)	108
Blood renal hypertension and renal extracts (1)	107
Blood renal hypertension and unilateral nephrectomy (1)	107
Blood serum and acetylcholine synthesis (1)	106
Blood serum, bone marrow-spleen immune and spleen cytology (3)	207
Blood serum cytotoxic and wound healing (3)	195
Blood serum electrophoretic changes and injury (2)	135
Blood serum glutamic acid content of (2)	159
Blood thromboplastic properties of mercurial diuretics (1)	69
Blood vascular action of benadryl (1)	78
Blood vascular nerves and benzyl imidazole (3)	161
Blood vascular reactions with photoelectric plethysmograph (1)	45

Frostbite and superficial minute blood vessels (1)	25	Insulin fibril formation (1)	111
Frostbite, pathology of (4)	220	Insulin level and lipogenesis (2)	157
G		Insulin, loss of potency of (3)	181
Camelocytes in vitro development of (3)	164	Insulin production by perfused pancreas (1)	2
Gastric secretion after introduction of fluids into intestine (1)	30	Insulin resistance in ovis (3)	201
Gelatin gels, melting points of (2)	136	Intestinal activity and antihistamine (1)	43
Gluconic acid in polyacetaldehyde of moss (2)	160	Intestinal activity effect of antispasmodics and nembutal on (1)	101
Glutamic acid decarboxylase in plants (2)	132	Intestinal mucosa, color of, affected by food and psycho stimuli (1)	30
Gonad pituitary relationship (1)	43	Intestine benzilate and activity of (3)	210
Gonadotrophins, antihormone reactions of (1)	34	Intestine, electrical and mechanical events in (1)	116
Gonadotropic therapy complicated by antihormone formation (1)	83	Intestine muscle histamine and potassium (3)	169
Gramicidin formaldehyde derivatives of (2)	134	Intrathoracic pressure, circulatory effects of local variations in (1)	11
Granulocytes amino acids in production of (2)	142	Irradiation and pharmacodynamic reactions (1)	69
Gravity forces effects of (1)	80	K	
Gravity tolerance of man (1)	59	Kidney activity and blood pressure (1)	89
Growth, caloric intake and protein utilization (5)	295	Kidney bound amino N in urine (2)	118
Growth, excess nicotinamide and (5)	231	Kidney diuresis by intravenous infusion of urine (1)	65
Growth factor essential (2)	137	Kidney excretion and reabsorption of bicarbonate (1)	82
Growth factor in cow manure (2)	151	Kidney excretion in alkaptonuria (2)	136
Growth inhibition with methionine sulfoxide (2)	123	Kidney excretion of cinchon alkaloids (1)	49
Growth of deficient diet by use of hydroponics (5)	236	Kidney excretion of corticoid hormones (2)	159
Growth of entameba histolytica (3)	177	Kidney excretion of mercury (3)	197
Growth, testicular atrophy and tocopherol (4)	224	Kidney excretion of thiamine and pyrimidin (2)	128
Growth, unidentified essential factor for (2)	128	Kidney function and hypertension (1)	58
H		Kidney function and response to pressure breathing (1)	24
Hearing loss from exposure to loud tones (1)	22	Kidney function in rats (1)	66
Heart and lungs transport of T 1524 and radioactive red cells through (1)	23	Kidney function influenced by water, anaesthetics and diuretics (1)	29
Heart and respiratory movements, Roentgen kymographs of (1)	10	Kidney glomeruli permeability for proteins (4)	227
Heart and vascular inflammation non bacterial (4)	225	Kidney hyalinized glomeruli by administration of urethane (4)	220
Heart border motion electrokymographs of (1)	9	Kidney ischemia damage (1)	80
Heart, cardiac component of orienting reflex (1)	87	Kidney metabolism in renal hypertension (1)	84
Heart chloroform action on (3)	196	Kidney output of amino acids with carbohydrate feeding (2)	118
Heart electrogram after physostigmin (3)	170	Kidney renal clearance of thiosulfate (1)	33
Heart electrogram in man cyanide and (3)	212	Kidney renin and constriction of opposite renal artery (1)	108
Heart failure and its mechanical efficiency (1)	63	Kidney scorbutic and alanine oxidation (2)	152
Heart failure and mercurhydriin (3)	193	Kidney tubule secretion of creatinine (2)	123
Heart, fatigued and cardiac glycoside (3)	200	L	
Heart, fibrillation and standstill in (1)	41	Lactic acid microdiffusion method in analysis (1)	65
Heart frog response to barbiturates (3)	181	Lactone antibiotics (3)	191
Heart glycogen and blood ketone levels (1)	69	Leg deformity in brooder raised chicks (1)	39
Heart irregularities and chloroethyl amine (3)	195	Leucopenia, transient method of observing (1)	25
Heart, isolated and adenosine-triphosphate (3)	170	Leukocytosis promoting factor of exudates (4)	226
Heart isolated and ethyl alcohol (1)	109	Lipid mustard compounds (2)	153
Heart lung preparation and dimethylamino-ethanol (3)	177	Lipids photolytic from visual pigments (1)	9
Heart muscle adenosine triphosphate activity of (3)	169	Lipids tissue, in essential xanthomatosis (4)	223
Heart muscle and coumestrol (3)	188	Lipids tissue, on low fat diet and chylous ascites (5)	233
Heart output by ballistic method (1)	76	Lipoprotein of egg yolk (2)	133
Heart pulse volume determinants (1)	62	Lipotropic factors (2)	145
Heart Q T interval in various species (1)	87	Lipoxidase soybean, activator for (2)	120
Heart recovery index factors in (1)	63	Lipoxidase, soybean and hemin proteins (2)	141
Heart response to abrupt deceleration (1)	55	Liver anaerobic glycolysis in (1)	110
Heart stroke volume arterial uptake and pressure pulse contour (1)	85	Liver and plasma phospholipid turnover in (4)	218
Heart tachometer for continuous recording (1)	102	Liver function tests (4)	225
Heart toxicity of local anesthetics (3)	166	Liver glycogen anoxia carbon dioxide and (1)	76
Heart work turbulent flow factor in (1)	107	Liver injury and splitting of acetylcholine (3)	163
Heat acclimatization to (1)	94	Liver phospholipid synthesis (2)	133
Heat and humidity air movement and human response to, (1)	70	Liver slices cholesterol synthesis in (2)	151
Heat and humidity extreme effects on man (1)	104	Liver tumor effects of copper on (5)	239
Heat death and injury, toxic factor in (1)	43	Lysine colorimetric method for (2)	148
Heat loss by air movement in clothed and nude men (1)	76	Lysine estimation with decarboxylase (2)	137
Heat loss by man, measurement of (1)	40	Lyszyme, properties of (2)	119
Heat thermal balance of men working in severe (1)	58	M	
Hemoglobin-saline solutions used clinically (1)	2	Malaria and liver function (1)	112
Hexylamines potentiating and pressor action of (1)	63	Malaria and P falciparum (3)	184
Histamine anti and anti anaphylactic agent (1)	202	Malaria and serum proteins (2)	153
Histamine anti pharmacology of (3)	176	Malaria detection of trophozoites of (3)	165
Histamine drugs anti and bronchial spasm (3)	144	Malaria metabolic products of antimalarials (2)	131
Histamine oxidase (2)	200	Malaria pamaquin and (3)	165
Hormone, adrenocorticotrophic assay of (3)	200	Malaria parasite and increased oxygen pressure (1)	82
Hormone pituitary adrenocorticotrophic (3)	16	Malaria, work capacity after recovery from (1)	45
Hormones sex, effect of, on castrate female chimpanzees (1)	3	Malarial drugs anti factors affecting (3)	163
Human centrifuge operation (1)	205	Malarial immunization in animals (6)	247
Hydantoinates anticonvulsant (3)	67	Mercury poisoning renal lesions in and BAL (4)	221
Hydrogen ion indicators and buffers slide rule for (1)	81	Metabolism, ascorbic acid and tyrosine (2)	121
Hydrogen ions and titratable acid in urine (1)	155	Metabolism carbohydrate and mustard vapor (3)	176
Hydroxyketo acids (2)	43	Metabolism carbohydrate, and uncoupling of phosphorylation (1)	99
Hypotension reactions to cross transfusion (1)	30	Metabolism iodine influence of thyrotropin on (1)	106
I		Metabolism nitrogen, and dietary factors (5)	240
Icterus physiologic of newborn (1)	249	Metabolism, nitrogen after trauma (1)	91
Immunochemistry of blood group A(6)	225	Metabolism nitrogen balance (2)	140
Influenza A virus infection (4)	99	Metabolism of aminobenzoic acid (2)	154
Inhibition azide of synthetic activity (1)	189	Metabolism of aminofluorene (2)	160
Insulin action (3)	47	Metabolism of androsterone (2)	145
Insulin and organic phosphates (1)	131	Metabolism of cinchonine (2)	119
Insulin and oxygen consumption by liver slices (2)			

Metabolism of dehydroisandrosterone (1)	40	Pamaquin, occurrence of leucopenia (3)	217
Metabolism of excess nicotinamide (2)	131	Pamaquine naphthoate as malarial prophylactic (3)	244
Metabolism of isopropyl alcohol (3)	169	Pamaquine, quinacrine, quinine bisulfate and plasmodium infection (3)	210
Metabolism of pregnenolone (1)	79	Pamaquine with quinine, methemalbuminemia (3)	167
Metabolism, oxidative pathway for pyruvate (2)	120	Pectinesterase specificity of plants (2)	145
Metabolism, porphyrin, and dietary protein (6)	237	Penicillin, action of (2)	142
Metabolism, tissue, and physiological activity (1)	67	Penicillin in lobar pneumonia (6)	256
Metrazol as antidote for pentothal (3)	215	Penicillin resistance of gram negative bacilli to (6)	253
Metrazol, central excitatory effects of (3)	208	Penicillin sensitivity of staphylococcus (6)	252
Methods, improvements in (2)	135	Penicillin toxicity of (1)	63
Milk, fluorine of, and dental caries (1)	67	Phlebitis, jugular (4)	274
Morphine addiction and conditioned responses (3)	213	Phlogene and exercise, blood gases and alveolar air after (1)	31
Morphine addiction and detoxication (3)	212	Physiological standards (1)	61
Muscle and nerve changes in prolonged hypertension and contracture (1)	34	Pituitary and sodium chloride, diuretic actions of (3)	179
Muscle changes related to pressure (1)	63	Pituitary extract, assay of (3)	162
Muscle, cutaneous, radiant thermal stimulation of (1)	114	Pituitary, renotropic effect of (2)	137
Muscle denervation atrophy and massage (1)	102	Plasmochin and sympathetic reflexes (3)	193
Muscle fatigue, factors in (1)	39	Plasmochin antimalarial clinical use of (1)	19
Muscle, frequency intensity curves in denervated (1)	67	Plasmaquin in plasmodium infections (3)	185
Muscle innervation, delimitation of (1)	71	Poliovirus, spinal fluid protein in (4)	218
Muscle membrane during contracture (1)	65	Poliovirus virus and deficient diet (3)	234
Muscle, oxygen consumption in stimulated, rapid bursts of in (1)	21	Posture autonomic and electroencephalographic effects of (1)	21
Muscle proteins in muscular atrophies (1)	27	Potassium, human tolerance to (1)	54
Muscle response to acetylcholine and potassium (1)	18	Pregnenolone anticonvulsant effect of (1)	71
Muscle, scorbutic, phosphates in (1)	49	Priscol cholinergic action of (3)	216
Muscle, smooth, adenosinetriphosphatase activity of (3)	202	Prostigmine action of (3)	198
Muscle, speed of movement and nutritional state (1)	96	Prostigmine elimination of (3)	199
Muscle triceps surae, stimulation of (1)	109	Protein hydrolyzates in intravenous feeding (2)	134
Muscle, working, and methemoglobinemia (1)	104	Protein hydrolyzates oral administration of (1)	14
Mustards, vesicant nitrogen and sulfur, effects of (4)	221	Protein intake and pyridoxine deficiency (5)	229
Myosin atpase, activation of (1)	13	Protein action of tyrosine on (1)	96
N		Proteins streptogenin and nutritive properties of (5)	243
Neostigmine, epinephrine and piperidines interactions of (3)	209	Protoporphyrin determination (2)	135
Nerve activity, role of acetylcholine in (1)	75	Pyrogen of bacterial polysaccharide (1)	6
Nerve and muscle tetraethyl ammonium bromide and (3)	161	Q	
Nerve axon acetylcholine formed by acetylase (2)	122	Quinine avitaminosis and motility (2)	142
Nerve axon permeability to fluorophosphate (3)	109	R	
Nerve cells, humoro electrotonic activity of (1)	32	Radar measurements of rates of free falling bodies (1)	40
Nerve conduction and fluoro phosphate (3)	172	Radioactive ions and placental permeability (1)	113
Nerve, DC potentials and dysfunction of ulnar (1)	36	Radioactive iron absorption of (5)	231
Nerve degeneration and regeneration (1)	25	Radioactive iron in study of iron metabolism (2)	130
Nerve deprived of blood supply (1)	37	Radioactive iron, utilization of (4)	219
Nerve fibres, cholinesterase in (1)	91	Radioactive isotopes and radiation of specific tissues (4)	222
Nerve ganglia and sympathomimetic amines (3)	192	Radioactive methods in following intravenous colloidal particles (4)	227
Nerve ganglion, action of ammonium bromide on (3)	197	Radioactive phosphorus after thyroparathyroidectomy (2)	159
Nerve ganglion depression with piperidines (3)	186	Radioactive phosphorus and phosphate exchange in bone (2)	133
Nerve neurons, action of adrenalin and acetylcholine on (1)	100	Relaxation, latency (1)	91
Nerve neurons, deafferented, and inherent tonus (1)	55	Respiration and circulation after intravenous nitrogen (1)	46
Nerve, origin of spike potential of (1)	8	Respiration, breath holding time (1)	63
Nerve properties near killed tissue (1)	59	Respiration effect of methemoglobinemia on (3)	212
Nerve, resting potential of, and sulfanilamide (1)	93	Respiration, intrapulmonary mixing curves and (1)	6
Nerve spinal cord, asphyxia and depolarization in (1)	41	Respiration, pressure volume diagram of thorax and lung (1)	62
Nerve spinal cord division, status of man with (1)	82	Respiration, treatment of carbon monoxide asphyxiation (3)	209
Nerve spinal cord reactions to laminectomy (1)	80	Respiration voluntary ventilation capacity (1)	35
Nerve spinal cord transection and reflexes below (1)	91	Respiration with intravenous NaCN (1)	49
Nerve spinal reflex patterns (1)	98	Respiratory ability of anesthetized men to breathe against pressure (1)	1
Nerve sympathetic ganglion cells, after discharge from (1)	60	Respiratory alveolar air and performance (1)	77
Nerve muscle transmission, fluorophosphate and, in myasthenia gravis (3)	182	Respiratory and circulatory response to oxygen (1)	24
Nervous system and oxygen consumption (1)	11	Respiratory asphyxia of newborn and pentobarbital (1)	97
Neurohumoral stimulation intra and extracellular pH in (1)	27	Respiratory breath holding time in anxiety states (1)	74
Neutron activation of tissue elements (1)	20	Respiratory exchange after pancreatectomy and evisceration (1)	62
Nicotinamide and carbon tetrachloride poisoning (2)	149	Respiratory half-centers, interplay of (1)	96
Nutrition and choline related compounds (5)	235	Respiratory negative mask pressure in free falling (1)	114
Nutrition, effects of choline on (6)	243	Respiratory partial pressures in alveolar air (1)	87
Nutrition, effects of streptomycin on (3)	177	Respiratory resuscitation from carbon monoxide asphyxia (1)	92
Nutrition in children of Mexico City (5)	235	Respiratory system, mixing gases in, with nitrogen meter (1)	64
Nutrition of mother and hydrocephalic young (5)	238	Respiratory water loss at altitude (1)	71
Nutrition, over, and ketosis (2)	141	Riboflavin metabolism after trauma and in convalescence (1)	3
Nutrition, problems of world (5)	232	Ricinolate after feeding, fate of (2)	149
Nutrition survey in Puerto Rico (5)	239	S	
Nutritional improvement of cereal flours and grains (5)	241, 242	Salicylamide, toxicity and analgetic potency (3)	162
O		Salicylate fractions in urine (3)	203
Obesity, activity and development of (1)	12	Salicylates, pharmacology of (3)	203
Obesity, oxygen consumption in (1)	12	Salicylates, prothrombinogenic action of (3)	221
Oubain elimination and nephrectomy (3)	187	Sarcosine, effects of (3)	101
Oxidase, l-hydroxy acid (2)	122	Sarcosine, effects of (3)	101
Oxidation, acetoacetate, intermediates of (2)	126	Sensory discrimination, two basic mechanisms of (1)	249
Oxidation reduction of methylene blue and orcein (3)	205	Serum antifibrinolysin (6)	177
Oxygen, high pressure of, and motor disability (1)	6	Serum, bone marrow immune, and trypanosoma infection (3)	132
P		SH compounds, color reaction of (2)	56
Pain, analgesic action of propane (3)	178	Shock, anaphylactic, blood studies in (1)	38
Pain, referred somatic, without segmental pattern (1)	106	Shock, concussion, cerebral lactate acid and phosphates in (1)	226
Pain thresholds and intravenous histamine (1)	89	Shock, damage to myocardial capillaries and (4)	62
Pain thresholds and neostigmine (3)	202	Shock, electric, benzedrine treatment of (1)	105
Pain, traumatic, factors in (1)	111	Shock, electro, seizures (1)	113
Pamaquin and hemolytic anemias (3)	176	Shock, hemorrhagic, alkalinizing agents in (1)	
Pamaquin, antimalarial activity of (3)	207		
Pamaquin metabolism influenced by quinacrine (3)	185		

Shock hemorrhagic and ischemic electrocardiographic changes in (1)	70	Toxicity of pentobarbital with succinate (3)	187
Shock, hemorrhagic and renal function (1)	92	Toxicity of pyribenzamine (3)	192
Shock, hemorrhagic morphine sensitivity during recovery from (1)	91	Toxicity of stilbamidine (3)	201
Shock, hemorrhagic portal pressure gradients in (1)	113	Toxicity of urea stilbamides (3)	197
Shock, hemorrhagic treatment with antihistamine (1)	50	Toxin of hemolytic streptococcus resistance to (3)	160
Shock, ischemic compression toxic factor in (1)	36	Tremor static production of (1)	72
Shock, post traumatic anuria in (1)	19	Trypsin activity iodination and (2)	124
Shock, tourniquet capillary circulation in (4)	217	Tuberculosis nucleoprotein from bacilli of (2)	129
Shock, traumatic afferent nervous factor in (1)	110	Tuberculosis serum proteins and carbohydrate in (2)	153
Shock, traumatic, local processes in (1)	83	Tularemia <i>B</i> , susceptibility to (6)	246
Shock, traumatic toxic factor in (3)	100	Tumor chicken latent period of (3)	169
Skin, intradermal wheals (3)	194	Tumor implants hyperemia around (4)	226
Skin penetration of mercury (2)	143	Tyramine, in vitro oxidation of (3)	260
Smoke cigaret effect of on rats (3)	151	Tyzer's disease of mice (4)	226
Sodium succinate as anesthetic in man (1)	15		
Spermatozoal phosphatase activity of (1)	67	U	
Spinal cord injury by gunshot wounds to vertebrae (1)	11	Ulcer prevention of, by intestinal extracts (1)	37
Starvation in man and metabolism (1)	53	Urea synthesis amides in (2)	120
Starvation semi and excretion of vitamins (1)	73	Uremia by protein depletion (1)	30
Starvation semi and gastric emptying (1)	45	Urethanes substituted phenolic (3)	184
Starvation semi and oxygen intake (1)	104	Uric acid formation in grasshopper egg (1)	9
Starvation semi and work capacity (1)	95	Uropepsin elimination due to diet (1)	14
Starvation semi electrocardiographic changes (1)	45	Uterine antispasmodics (3)	183
Starvation semi, specific gravity and body fat (1)	16	Uterine motility activated by ciliopath (1)	79
Starvation survival and metabolic rate (1)	56	Uterus electrophysiology of (3)	215
Steroid excretion (2)	137	Uterus, in vivo motility of (3)	172
Steroids 17 keto (1)	43	Uterus irritability of (3)	171
Stilbestrol monomethyl ether (1)	15	Uterus pregnant, inhibition by epinephrin and hypogastric stimulation (1)	23
Stomach acidity influence of wine on (1)	77		
Stomach and intestinal motility after hemorrhage (1)	75	V	
Stomach calcium in mucus of (1)	49	Vaccine typhus rickettsial antigen from (2)	129
Stomach emptying and anoxic anoxia (1)	60	Vaccines allergic and anaphylactogenic properties of (6)	245 252 254
Stomach emptying time and chloral hydrate (1)	77	Vaso-depressor compounds pharmacology of (1)	60
Stomach potentials origin of, between submucosa and mucosa (1)	85	Venom scorpion physiological actions of (1)	23
Stomach secretion and carbon dioxide (3)	183	Virus and vaccines of influenza (6)	254
Stomach secretion of and endocrines (1)	54	Virus influenza and ultraviolet irradiation (6)	248
Stomach intestine absorption of iron ferritin and (2)	136	Virus inhibition of glucose use by brain (6)	252
Streptomycin bacterial action of (6)	247	Virus papilloma, of rabbit (6)	245
Streptomycin promin and tubercle bacilli (3)	204	Virus poliomyelitis from stools (6)	250
Streptothricin and anatomic changes (3)	194	Viruses bacterial activated by amino acids (1)	2
Sulfanilamide in biological samples (1)	190	Viruses of infectious hepatitis and serum jaundice (6)	248
Sulfathiazole and <i>n</i> propyl carbamate on bacterial life (1)	27	Viruses pneumotropic in respiratory disease (6)	249
Sulfathiazole penetration into cerebrospinal fluid (3)	207	Vitamin A, absorption of in ester and alcohol forms (2)	129
Sulphadiazine response to (3)	174	Vitamins A ₁ and A ₂ in retina (2)	153
Sweat and work chloride and nitrogen balance (5)	234	Vitamin A determination (2)	155
Sweat glands functional count of in man (1)	84	Vitamin A in fish liver oils (2)	155
Sweat salt content and work (5)	230	Vitamin A levels in plasma (1)	74
Sweat secretion decline of men working in heat (1)	37	Vitamin A pro requirement of hens (5)	243
Sympathectomy and control of circulation (1)	56	Vitamin A storage and diet (2)	148
Sympathetic-mimetic drugs synergism between (1)	194	Vitamin A storage beta-carotene and (2)	127
Sympatholytic agents (3)	195	Vitamin ascorbic acid distribution in blood (2)	151
Synovial fluid, dynamics of (1)	85	Vitamin ascorbic acid in raw carrots (5)	233
Syphilis serologic tests for (6)	251	Vitamin ascorbic acid metabolism of (5)	238
		Vitamin B and carbohydrate utilization (1)	38
		Vitamin B studies with different carbohydrate diets (5)	240
		Vitamin B ₆ bioassay (5)	239
		Vitamin biotin affinity of avidin for (2)	160
		Vitamin biotin deficiency (5)	232
		Vitamin biotin in tissue metabolism (2)	143
		Vitamin biotin in treatment of progressive paralysis (5)	240
		Vitamin C of orange juice (5)	230
		Vitamin D ₂ massive doses of (2)	148
		Vitamin niacin deficiency failure to produce (5)	230
		Vitamin nicotinic acid excretion (5)	231
		Vitamin nicotinic acid excretion and tryptophan (2)	154
		Vitamin pantothenic acid storage in mouse (5)	229
		Vitamin pantothenic acid, tissue and diet (5)	237
		Vitamin pyridoxine deficiency (4)	222
		Vitamin pyridoxine deficiency and resistance (5)	229
		Vitamin riboflavin deficiency and carbohydrate metabolism (5)	236
		Vitamin riboflavin excretion and nitrogen balance (5)	237
		Vitamin riboflavin from yeasts (5)	238
		Vitamin riboflavin urinary excretion of (5)	228
		Vitamin thiamin from yeasts (5)	236
		Vitamin thiamine in rice (5)	235
		Vitamin thiamine requirement of infants (2)	138
		Vitamin utilization in lactating women (5)	239
		Vitamins B effects of on proteinases (4)	223
		Vitamins renal excretion of (2)	139
		Venoms snake and prothrombin time (1)	68
		Vomiting intravenous glutamic acid inhibition of (1)	89
		W	
		Water loss xanthines pituitary and (3)	178
		Wound potential and healing agents (1)	4
		X	
		X ray diffraction in gallstones (2)	155

ABSTRACTS APPROVED BY THE SECRETARIES RECEIVED TOO LATE FOR PRECEDING ISSUE

PHYSIOLOGY

Influence of over-ventilation on the cardiovascular reflexes of carotid sinus origin C HEYMANS, R PANNIER and A VAN OSTENDEL *Department of Pharmacology, University of Ghent, Belgium* In previous experiments (C Heymans, J J Bouckaert and A Samraon, *Arch intern pharmacodyn* 18: 157, 1934) we were able to show that apneic blood has no influence either on the tone or reflex excitability of the vagal and sympathetic cardio regulatory centers, or on the peripheral excitability of the vagal and sympathetic innervations regulating the heart rate.

Carbon dioxide is considered as necessary for the normal function of the vasoconstrictor center. The influence of over ventilation on the vasomotor reflexes of carotid sinus pressosensitive origin was investigated in a number of vagotomized dogs anesthetized with chloralose. The efferent arteries of both carotid sinuses were ligated, care being taken not to sever the pressosensitive innervation. The cephalic ends of the common carotid arteries were connected with a pressure device. By means of this technique, the hydrostatic pressure may be increased or decreased in the circulatory isolated but only pressosensitive innervated carotid sinus. The reflex influences on the peripheral vasomotor tone and on the general blood pressure were registered both under normal artificial respiration and during over-ventilation.

We have observed that over ventilation, induced by artificial respiration with a fast rate but with a normal stroke, provokes in the majority of the animals only a slight or no fall of the blood pressure, although the over ventilation caused a marked alkalosis, tetany and prolonged apnea. If, during the over ventilation, the intra carotid sinus pressure was raised, a very marked peripheral vasodilatation with a deep fall of the general blood pressure occurred. The reflex vasodilatation and fall of blood pressure were identical with the normal reactions occurring in the same animals under normal pulmonary ventilation. From these and previous experimental observations it is concluded that the carbon dioxide of the blood is not necessary for the maintenance of the tone and the reflex excitability of the vasomotor and cardio regulatory centers.

Influence of the anticholinesterase (prostigmine), atropine and acetylcholine on the cardio-vascular and respiratory centers C HEYMANS, R PANNIER and R VERBEKE *Department of Pharmacology, University of Ghent, Belgium* In dogs, under complete chloralose anesthesia, the efferent

vascular branches of both carotid sinuses are tied at their origin, care being taken not to sever the pressosensitive innervation of the carotid sinus. The cephalic ends of the common carotid arteries are connected with a pressure device. By means of this technique, the endovascular pressure may be increased or decreased in the circulatory isolated but pressosensitive innervated carotid sinus. The cardio vascular and respiratory reactions of the animal to the intracarotid sinus pressure changes are registered before and after administration of prostigmine. Doses of prostigmine inhibiting nearly completely the cholinesterase activity of blood serum and blood corpuscles do not stimulate the respiration but may increase the vagal heart slowing induced by an increase of the carotid sinus pressure, while the reflex vasodilatation and the reflex respiratory inhibition are not affected.

In a second series of experiments, the isolated cephalic circulation of a dog B is perfused by means of a dog A, the vagalortic nerves connecting only the isolated perfused head of dog B with his trunk which is kept alive by means of artificial respiration. The activity of the respiratory center of the perfused head B and the heart rate of trunk B are registered. Injections of the anticholinesterase prostigmine in the donor dog A, or directly into the isolated cephalic circulation of dog B, do not increase the reflex excitability of the respiratory and cardio inhibitory vagal centers of head B towards rises of blood pressure in the carotid sinus or cardio aortic pressosensitive areas. Injections of prostigmine into the circulation of the trunk of dog B may on the contrary increase the cardio-inhibitory vagal response in trunk B induced reflexly by a rise of blood pressure in the carotid sinus of the perfused head B.

Injections of atropine into the isolated perfused cephalic circulation of dog B do not affect the excitability of the respiratory and cardio inhibitory vagal centers towards reflex stimulations of carotid sinus or cardio aortic origin. Atropine, acting on the cardio inhibitory center only, also does not affect the direct excitability of this center towards nicotine or acute anemia.

Injections of acetylcholine into the cephalic perfused circulation provoke an intense stimulation of the respiratory and cardio inhibitory centers. These stimulations are mainly of a reflex origin and are due to the excitation by acetylcholine of the chemoreceptors of the carotid glomus. After exclusion of the carotid chemoreceptors of the perfused cephalic circulation, only very high doses of acetylcholine have a direct stimulating

effect on the respiratory and cardioinhibitory vagal centers. These reflex and direct central effects of acetylcholine are not affected by the central action of atropine. Prostigmine inhibits the destruction of acetylcholine and thus increases the reflex and central effects of acetylcholine on the respiratory and vagal centers. The reflex excitation of the respiratory center induced by means of other stimulants of the chemoreceptors of the carotid glomus is however not increased by the anticholinesterases eserine or prostigmine.

These different experimental observations concerning the influence of the cholinesterase prostigmine, of atropine and acetylcholine on the reflex and direct excitability of the vasomotor, respiratory and cardioinhibitory vagal centers are not in favor of the theory of the role of a cholinergic chemical mediator in the transmission of excitations in these parts of the central nervous system.

Protection against acceleratory forces by CO₂ inhalation. L. VAN MIDDLESWORTH (by invitation) and S. W. BRITTON. *Physiological Laboratory, University of Virginia Medical School.* Increased tolerance to positive acceleratory forces has been demonstrated with monkeys, cats, and dogs which inhaled CO₂/O₂ mixtures before and during the acceleration. Bilateral uterine pressure, LKGr, and LEG were continuously recorded in more than 200 exposures of 30 animals. 13-20% CO₂ in O₂ administered (at sea level) to monkeys for 18-180 seconds, or to dogs 50-180 seconds, prevented about 40% of the blood pressure changes ordinarily observed at 4 "g" per 10 second exposure. When this mixture was inhaled for more than 300-400 seconds the beneficial effect was lost.

PHARMACOLOGY

Measurement of cerebral blood flow and cerebral oxygen consumption in man. SEYMOUR S. KATZ and CARL F. SCHMIDT. *Laboratory of Pharmacology, University of Pennsylvania, Philadelphia.* (Motion picture demonstration.) The course of an experiment is shown in which the nitrous oxide method (Am J Physiol 143:53, 1945) was used to estimate the effects of inhalation of 10% O₂, which were to increase cerebral blood flow by 35% with no change in cerebral O₂ uptake while mean blood pressure (directly recorded) fell 10 mm. Part of a similar experiment is shown in which pentothal intravenously in light anesthetic dosage decreased cerebral blood flow by 34%, decreased cerebral O₂ uptake by 44% and did not change blood pressure. In another experiment radioactive krypton (Kr*) and N₂O were inhaled successively and the flow estimated from blood samples taken during saturation with N₂O was compared with that calculated from other samples collected during desaturation with Kr*. The two were identical,

indicating that the solubility coefficient of Kr* in the brain in vivo is the same as that of N₂O. At the same time the Kr* in the brain was measured directly and the flow calculated from this and the A-V Kr* difference was found to agree closely with that estimated from the A-V N₂O differences.

Cardiovascular effects of certain aliphatic sympathomimetic amines. DAVID I. MARSH (introduced by C. D. Leake). *Dept. of Pharmacology, School of Medicine, West Virginia University, Morgantown.* 1. Hexylamine, 2. heptylamine, 1-methyl-2-hexylamine, 1-methyl-2-heptylamine, 5-methyl-2-heptylamine, 2-heptylamine ("Tumamine"), 1-cyclopentyl-2-propylamine, and 2-cyclohexylethylmethylamine were administered intravenously to urethane- or barbitalized dogs. Some animals also received atropine or scopolamine and morphine. Photokymographic records of femoral or carotid arterial blood pressures were made with Hamilton Be-Cu diaphragm manometers. Some records were made of the right and left heart intraventricular blood pressures.

All of these agents increase the heart rate and produce a prompt, sustained rise in blood pressure on the administration of 0.1 to 5.0 mgm/kgm. These agents all antagonize the vasodilator activity of epinephrine and butamefrin. They are only poorly antagonized by yohimbine and piperidine-methylbenzodioxan (9331) and are never reversed like epinephrine. Repeated administration leads to transient tachyphylaxis although the effects of a previously standardized dose of epinephrine are unchanged. These aliphatic amines act additively with one another and with the phenalkylamines such as amphetamine and ephedrine. Mutual cross tachyphylaxis among them can be produced.

The rise in blood pressure is due primarily to peripheral vasoconstriction as indicated by the slope of the femoral arterial pulse contour. That the pulmonary vascular system is not constricted can be demonstrated from the right and left heart intraventricular pressure records.

The obvious conclusion concerning the mechanism of action of these agents is that, like amphetamine, they act directly on those sympathetic effector organs that do not act by way of a mediator.

NUTRITION

The effect of dietary restrictions and α -tocopherol on stomach lesions and body weight of rats. E. L. HOVE (by invitation), K. HICKMAN and P. L. HARRIS. *Research Laboratories, Distillation Products, Inc., Rochester, N. Y.* Stomach lesions in rats have been produced by feeding diets low in protein, essential fat acids, pyridoxine or calories. Intermediate degrees of restrictions induce rumen

lesions which in all cases are prevented by daily administration of α -tocopherol. Rigid restriction of Calories causes severe hemorrhagic lesions in the fundic area of the stomach which are less influenced by tocopherol treatment.

The loss in body weight of rats restricted to 10, 30, 20, 10 or 0 Calories daily of a diet complete in all factors, except vitamin B₁₂, can be influenced by several dietary variations. A fivefold increase in B complex concentration in the diet results in less rapid weight loss. α -Tocopherol fed either during or prior to restriction causes more efficient utilization

of the available food at the higher caloric levels and at either level of B complex supplementation. The type of fat in the diet has a marked influence on weight loss during restriction. Weight losses are least severe with hydrogenated coconut oil in the diet, but increase as the unsaturation of the fat increases.

Although there are many apparently different and independent causes of stomach lesions all of these may operate through their effect on amino acid metabolism.

CORRECTIONS OF ABSTRACTS IN PRECEDING ISSUE

Page 17 Clark and Jorgenson, and the following abstract by Clark, Gardner, McIntyre and Jorgenson, where the word gram/s is printed it should read "g" meaning gravity acceleration.

Page 31 Giddston and Iuetscher, in paragraph 2, line 1, change 15 to "21", 12 to "17", line 2, change 97 to "99", in line 3, change 96 to "98", in line 4, change 1 to "11", line 5, change 1 to "9", in line 6, change 110 to "98", 125 to "122", 117 to "114", in line 7, change 103 to "92", 123 to "118", in line 8, 111 to "110". In paragraph 3, line 1, change 10 to "9", line 3, change 8 to "7", in line 11, 105 to "103".

Page 35 Greeley, Jorgenson, Clark, Drury and Henry, where the word gram/s is printed it should read "g" meaning gravity acceleration.

Page 41 Hamilton and Remington. Correct title to read "Comparison of the time concentration curves in arterial blood of dye injected at a constant rate with that of dye injected instantaneously."

Page 41 Harris. Correct title to read "Ventricular fibrillation and standstill in coronary occlusion, anoxia and hemorrhagic shock." Also in the last line of the first paragraph and in the first line of the fourth paragraph the word hemorrhage should be replaced by the words "hemorrhagic shock."

Page 68 Macht. The word optical in the tenth line of the next page should read "optimal."

Page 69 Macht (second column). Add the words "after treatment, concomitant with clinical improvement" to the last sentence.

Page 74 Mirsky, Iipman and Grinker, the origin of this report should be credited in part to the Department of Psychiatry, Michael Reese Hospital, Chicago.

Page 81 Pinson and Chapamis. The word requiring in the last sentence should read "requiring."

Page 84 Raska. The last paragraph should read "It was found that the increase in antihyperten-

sive activity of these extracts was due to an increase of both dialyzable and non dialyzable blood pressure lowering fraction. Under the experimental conditions the increase due to the dialyzable fraction was greater than that due to the non dialyzable fraction. Hypotensive substances of renal origin are probably the products of oxidative processes. They are formed in increased amounts in the compensating kidney."

Page 91 Scarff and Pool. In the first and fourth line of the third paragraph the word three should read "two."

Page 111 Klein and Hurwitz. Line 6 (in second column) should read "per kg and 32 mg per 100 gm 32 minutes after."

Page 162 Ambrose and De Leds. The word barbitol (line 5, second column) should read "barbital."

Page 167 Blake, Zubrod and Rosenfeld. The next to the last line in the second paragraph should read "coefficient may be given as $\sum_{405 \text{ mu}}^{\text{mol}} = 80 \times 10^4$." The last two lines of the third paragraph should read "ranged from 3 to 25 mg of hematin per liter with an average of 16 mg per liter."

Page 183 Jarler, Zubrod, Rosenfeld and Shannon. Line 8 (on the next page) should read "quinacrine concentration from 59 to 142 gamma."

Page 191 McOmie. The following sentence should be added "Diethyl phthalate is not likely to present an industrial hazard."

Page 195 Nickerson, Namaguchi and Goodman. At the end of fourth line from the bottom of the first paragraph the word p-propyl should read "isopropyl." The following should be substituted for the last paragraph "In neutral or alkaline solutions the β chloroethyl chain of these compounds may perhaps close with the amine nitrogen to form a highly reactive ethylene imine ring which is then hydrolyzed to the inactive ethyl alcohol derivative with the release of HCl. Thiosulfate is known to react rapidly with such a

ring to form the ethyl thiosulfate derivative *in vitro*. Prior treatment of an animal with thiosulfate completely prevents the sympatholytic action, indicating that the same reactions may occur *in vitro*. The theory is presented that the ethylenimine ring compound is probably the intermediate directly involved in the blocking. It is possible that substitutions on the benzyl group or its replacement alter the sympatholytic properties of these compounds by an inductive effect modifying the ring formation."

Page 211 Way. Line 6 (on the next page) should read "lethal dose of isomiprone only, and the onset of death seemed to be"

Page 213 Wilson and De Lids. Seven lines from end, the word *fluorenone* should be "fluorenone."

Page 218 Andelman, Lushben and Casey. The work was done "Under the direction of Herman N. Bundesen."

Page 220 Ehrlich, Harris and Mertens. Delete the last sentence.

Page 239 Robinson and Suárez. The end of the last sentence of the second paragraph should read "calcium 59, protein 79, calcium 91, iron 15, vitamin A 81, thiamine 82, riboflavin 88, niacin 68 and ascorbic acid 58."

NOTES ON THE ATLANTIC CITY MEETING, March 11, 12, 13, 14, 15, 1946

The thirtieth meeting of the Federation was held at Atlantic City, N. J., on March 11-15, 1946, under the auspices of the five Philadelphia medical schools (Hahnemann, Jefferson, Pennsylvania, Temple and Woman's) and under the chairmanship of Dr. Philip Bard, President of the American Physiological Society. The first day (Monday, March 11) was devoted to registration and to meetings of the various councils. On this day there were also non-Federation sessions of the American Society for Cancer Research, an informal Conference on Poultry Nutrition, and a Symposium on Adrenal Cortical Hormones. Meetings of the six constituent societies began on Tuesday, March 12, at 9:00 A.M. and continued until Friday, March 15, at 5:00 P.M. The Physiological and Biochemical Societies each met in four sections, the Pharmacological Society in three, the Institute of Nutrition and the Pathological and Immunological Societies in one each. A total of nine symposia were presented, each society sponsoring at least one. All scientific sessions were held in the Atlantic City Convention Hall. At the request of the presiding officers the customary Federation Joint Session, Federation Banquet and Static Demonstrations were omitted. Entertainment was confined to two informal smokers at the Chelsea Hotel on Tuesday and Thursday evenings, to which tickets were sold at seventy-five cents each.

The total registration was 2309, of whom 1016 were members and 1293 non-members. A registration fee of \$2.00 was charged. The Local Committee received \$7906.26 and spent \$5515.62 leaving a balance of \$2390.64 for the Federation Treasury. 1150 copies of the Federation Program were sold at fifty cents each and 885 copies of the Federation Proceedings at \$1.50 each. The attendance at all the meetings was unusually large. Based on

previous experience, rooms seating 125 to 150 were provided for three of the Biochemistry and two of the Pharmacology sections and for all meetings (except the symposia) of the Institute of Nutrition and the Pathological and Immunological Societies. These rooms proved too small and larger ones were provided as far as possible. The Atlantic City meeting was memorable for several reasons.

1. It was the first to be held following the lifting of most restrictions on public presentation of work done in relation to World War II. The scientific sessions and symposia showed the strong influence of this factor.

2. It was the first meeting in four years. The pent-up desire for open meetings and discussions doubtless had important bearing on the unexpectedly large registration of Federation members.

3. It was the first meeting in which the American Association of Immunologists participated as a member of the Federation, thereby raising the number of constituent societies to six.

4. It was the first meeting held at a distance from a University or Medical Center. This probably accounts for the relatively large proportion of members of the Federation in the total attendance. It also marks recognition of the change of the Federation meeting from a small, compact, relatively informal affair to a complex function requiring the services and facilities of a professional convention bureau.

Significant actions by the Executive Committee and approved by all the constituent societies were

1. Approval of the purposes of the National Society for Medical Research which are designed to further popular education regarding the necessity, humane character and accomplishments of animal experimentation. Also approval of the

activities of the Friends of Medical Research in New York State

2 Decision to hold the 1917 Annual Meeting in Chicago from May 18 to 22 inclusive under the auspices of the University of Illinois, and to approve tentatively the holding of the 1918 meeting in New York City and the 1949 meeting in Detroit or San Francisco

3 Decision to raise the annual assessment per member in all constituent societies to \$2.00

4 Appointment of Dr William H Chambers of the Cornell University Medical College as Federation Secretary-Treasurer

5 Decision to hold a Joint Scientific Session at the next Annual (Chicago) Meeting with the Biochemical Society in charge of the program, with the proviso that no business would be transacted

6 The following Federation Standing Committees were appointed

Defense of Biological Research

A C Ivy, Chairman

K F Meyer

Ephraim Shorr

International Congresses

D W Bronk, Physiology, Chairman

A J Carlson, Physiology

D D Van Slyke, Biochemistry

E K Marshall, Jr, Pharmacology

Peyton Rous, Pathology

L A Maynard, Nutrition

J I Bronfenbrenner, Immunology

Placement Service

H B Lewis, Director

Representatives Council A A A S

G Philip Grabfield

C Glen King

Federation Proceedings Control Committee, as nominated by the respective societies

Philip Baird, Physiology, Chairman, term expires 1948

C G King, Biochemistry, term expires 1948

C F Schmidt, Pharmacology, term expires 1947

Morton McCutcheon, Pathology, term expires 1947

A H Smith, Nutrition, term expires 1949

A P Locke, Immunology, term expires 1949

The American Institute of Nutrition

SYMPOSIUM ON APPLICATIONS OF THE NEWER KNOWLEDGE OF NUTRITION TO PRESENT DAY PROBLEMS

WILLIAM C ROSE, CHAIRMAN

THE FOOD AND NUTRITION BOARD OF THE NATIONAL RESEARCH COUNCIL A REVIEW OF SOME OF ITS ACCOMPLISHMENTS AND A FORECAST OF ITS FUTURE

FRANK G BOUDREAU AND RUSSELL M WILDER¹

The exacting problems of today make it difficult to recapture the atmosphere which prevailed at the beginning of the war. The Axis powers in Europe in 1939 and 1940 were adding victory to victory, and the threat to this country of Japanese aggression was increasing by the hour. Steps to defend ourselves seemed to lag and each proposal to prepare for what appeared to be the inevitable involvement of this country was a target for attack by many ignorant, confused, or evil minded persons. Into this confusion came the clarifying call of President Roosevelt reassembling the National

Defense Advisory Commission which had not seen the light since World War I, but which at once began to plan to place this country in a position to defend itself against aggression.

It was in this atmosphere of crisis that the Committee on Food and Nutrition, later called the Food and Nutrition Board, met for its first sessions in November, 1940. Set up by the National Research Council at the request of the National Defense Advisory Commission, it was asked to mobilize the scientific knowledge of nutrition for the guidance of the several agencies of government which were facing problems which involved food and nutrition.

It was known in 1940 that Nazi Germany was vigorously applying the newer scientific knowledge of nutrition. The Germans were aware of the absolute necessity of preventing a repetition of their tragic failures on the food front during the first World War. Yet it seemed to be impossible for our

¹ Russell M Wilder was the first chairman of the Food and Nutrition Board and is now its vice chairman. When he resigned as chairman, he was succeeded by Frank G Boudreau. This paper was presented at the Atlantic City meeting of the American Institute of Nutrition on March 12, 1946 by Russell M Wilder.

statesmen to believe that food could play a decisive part in war for us. No serious plans for rationing were contemplated officially. Harassed as we had been by the problem of food surpluses, the very idea of shortage seemed purely academic. Although it was obvious to anyone with a little knowledge of engineering that the war would be won by the side which got there first with the greatest amount of equipment, no one gave much attention to the fact that stepping up the production of machines depended ultimately on stepping up the efficiency of men or that longer hours of labor and increased stress would create the need for proper feeding programs for the workmen. Although there was concern to develop special gasoline and fuel oil for the fighting planes, no one gave much thought to the fuel fed to the human engines who made those planes. Into this arena went one Committee of the Board with considerable effectiveness, so that by the time the war was at its height, so called in-plant feeding programs had been introduced in a very large proportion of American industrial organizations.

Many agencies became involved as other problems of nutrition became intensified by war. State nutrition programs were widely undertaken to explain rationing to the people and to encourage the improvement of food habits. The Red Cross developed excellent cooking classes with emphasis on the preservation of nutrient values. Better and more general public education in nutrition with extensive use of supervised advertising, donated by private industry, became the business of a group in the Federal Government, which later became the Nutrition Programs Branch of the War Food Administration. By 1943 special cognizance was taken of the food needs of civilians by a Civilian Food Requirements Branch of the Food Administration, and the Army in the meantime had overcome an earlier indifference to the science of nutrition and was basing its enormous program of soldiers' rations on sound nutritional principles.

It is perhaps too early to appraise the contribution of workers in nutrition to the winning of this war, but some credit undoubtedly is due them for the fact that the country has come out of the war with unusually good health reports. Infant mortality has continued its decline despite the war, and in contrast to the usual experience in war, Deaths from tuberculosis have not increased as they always did before in war, indeed a new all time low record has been obtained. The figures for maternal mortality are better than they were before the war, and the same is true for virtually all death rates which reflect in any way the influence of diet on the public health. We might be less assured of the contribution of nutrition to these better records were it not that in Great Brit-

ain the fall in these rates has been even more pronounced, and over there all environmental factors except nutrition were worsened by the war.

If any part of this accomplishment is to be credited to the Food and Nutrition Board, it is due to its assistance and support from many sources: the unfailing helpfulness of Ros. Harrison and Robert Grigg, Chairmen respectively of the National Research Council and of the Division of Biology and Agriculture, the cooperation of the agencies of government with which the Board was working, the support received from industry, and above all else the help of the many scientific colleagues whose advice was sought with regularity and who frequently were asked to serve on the technical committee of the Board.

The conspicuous failures of the Board were two: an inability to effect more significant research, and smaller representation in its membership of scientists in nutrition than was necessary to justify the assumption that the Board could speak for the science of nutrition of this country.

The failure more effectively to stimulate research on civilian problems of nutrition was due to lack of funds. The few such projects which were sponsored by the Board were financed altogether by funds from private sources. Official understanding of the nature of "total war" went far enough to appreciate the need for applying current knowledge to the maintenance of civilian health, but not far enough to appreciate the need for spending money to investigate the nutritional requirements of civilians, nor even for research on problems relating to the efficiency of workers who were making the machines which won the war.

All committees of the National Research Council are appointed by the officers of the Council, and this was the procedure followed in the case of the Food and Nutrition Board. In making appointments to the Board the aim was to secure a group of persons who by virtue of special experience in nutrition combined with a judicial temperament could interpret for the Government the factual information then available. The science of nutrition covers many disciplines and so far as could be done these disciplines were represented in the membership. Committees function smoothly only when their members learn to think together. The Food and Nutrition Board had the usual difficult beginning but afterwards began to operate effectively enough to gain the confidence of several agencies of government. As this occurred, increasingly important problems were presented for its consideration, problems which in time of war had to be answered expeditiously or not at all. From this arose a hesitancy to change the working quality of the Board by introducing much new blood. The argument is no longer valid since the

war is over and changes in the membership are now being made

Despite the rigidity of the membership of the Board, new blood was introduced throughout the war period by frequent changes in the liaison membership, by organizing new committees or appointing new members on old committees, and by inviting members of committees to the meetings of the Board and asking them or other individuals to report new work or to review special fields. Also useful in the development of background for the deliberations of the Board was a regular report by the Committee on Food Supply as to amounts of food commodities available. This usually included a report on situations overseas. Likewise symposia on nutritional conditions in foreign countries and at home helped to build up a frame of reference for the Board's discussions.

To be noted is the extent to which the interest of the Board extended beyond the borders of this country. Two members were Canadians, and close liaison with Britain has been maintained through visitors in Washington from the Ministry of Food, the Medical Research Council, or the British Military Services. On frequent occasions persons holding similar positions in other foreign countries have attended meetings and have taken part in the discussions of the Board. On the other hand members of the Board have attended meetings of bodies dealing with nutrition in Canada and England and have served on a committee of the Combined Food Board, which reported on the wartime food consumption levels of Canada, the United Kingdom, and the United States. A group of members of the Board, and through them the membership as a whole, was in close touch with the preparation and conduct of the Hot Springs Conference of 1943, also with the work of the Interim Commission on Food and Agriculture which prepared the ground for the meeting in Quebec which set up the Food and Agriculture Organization of the United Nations.

The work of the Board is recorded in its minutes and reports. Stenotypists' notes are freely used in the preparation of its minutes and careful indexing of these minutes makes for ready access to past deliberations. The minutes of the Board have been distributed to interested agencies in this country and abroad. The reports of the Board, issued as publications in the reprints and circular series of the National Research Council, have a wide circulation. These reports cover dietary allowances, fortification and enrichment of food staples, the nutrition of industrial workers, the nation's protein supply, the composition of food, and allied subjects.

A further measure of the scope of the work of the Board is provided by the list of its committees

There were committees in 1945 on cereals, fats, milk, protein, dietary allowances, nutrition of industrial workers, international food problems, and research personnel. In addition, special committees were investigating nutritional aspects of ageing, dental caries, survey procedure, and other subjects.

The major part of the activities of the Board is obviously as important in time of peace as it has been in war, and when the war ended the question at once arose as to what should be done about their continuance. Indeed the question was what should be done with the Board. The wartime agencies of government with which the Board had worked were dissolving, and it was to be expected that the permanent duties of the members of the Board, to some extent neglected while the war was on, would leave less time for the work of the Board. Whatever might be contemplated, changes in the structure of the Board would be in order, and in the category of musts, if the Board was to continue to represent the nutritional science of this country, would be arrangements for tapping all sources of informed opinion, indeed for very close cooperation with bodies such as the Institute of Nutrition and other scientific societies.

The present planning contemplates continuing the Board with structural changes. The membership will be limited to 24, and members are to serve no longer than three years. Thereafter they will not be eligible for appointment until the lapse of a year. In preparation for a staggering of appointments, one third of the present twenty-one members have been given a one year term, another third a two year, and the balance a three-year term of office. A Steering Committee of seven members has been authorized by the Board to act for the larger body in the intervals between meetings which, by necessity, will be less frequent than during the war. Other committees have been reorganized with smaller memberships, and the duties of some of them have been redefined. Arrangements have been made to secure discussion of the more important problems by representatives of professional societies with interests in nutrition, and the advice of such societies is always to be sought when possible. Members of committees are to be listed in the future as panel members of the Board.

It is the business of government to develop and to implement nutrition policy, but the stuff from which sound policy is made can only come out of free discussion by the workers in the several fields of science encompassed by nutrition. It should be a responsibility of the Board to encourage the discussion of the basic facts affecting current policy and to transmit the results of such discussions to the government.

A great step forward in the application of good thinking in nutrition was taken when the United Nations Organization on Food and Agriculture selected Sir John Orr as its Director General. Sir John has called upon the member governments of this international body to set up national nutrition groups with functions comparable to those of Food and Agriculture Organization of the United Nations. Such a group or committee or council will have to be developed in this country. Indeed our government is expected to set the example in this matter. However, such a body composed largely of administrators will require scientific guidance of the type which the Food and Nutrition Board is particularly well qualified to provide.

A concern of those who labored to bring about the recently established United Nations Organization on Food and Agriculture has been to make clear that a primary responsibility of agriculture is the cultivation, not alone of corn or wheat or hogs, but of human health. Sir John Orr has emphasized that satisfaction of the human need for food is the best way, and perhaps the only way, to assure a strong enduring agriculture, and to

provide for the welfare of agricultural producers who constitute the majority of the world's workers.

This human need for food, however, has a very complex meaning, and those who are informed about this matter because of training in nutrition face the grave responsibility of bringing to our statesmen the information they must have to develop policies which will be based on human need. In matters such as this the Food and Nutrition Board, reconstituted as described above, can well serve as the mouthpiece of nutritional science. A major duty of this body ought to be the focusing of attention in official circles on those facts of science which the consensus of well informed opinion regards as indispensable for good nourishment. For only with such scientific guidance can food policy be directed to satisfying human needs.

During the war food supplies were managed in such a way as to meet human needs. The result was better health and probably some hastening of victory. Now that victory has been won, similar efforts to meet basic human needs for food will contribute substantially, we believe, to the building of lasting peace.

INTERNATIONAL FOOD EVALUATION ACTIVITIES AND PROBLEMS

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Wartime experience in interallied food planning, for the armed forces and for the civilian populations, gave rise to certain problems of food evaluation not previously appreciated by individual countries in dealing with their own supplies. These problems were first encountered in the joint studies¹ begun in London in 1943 by representatives of the United Kingdom, Canada and the United States, of the food supplies available in each country in relation to its nutritional needs. It early developed that, apart from inherent differences in the food supplies themselves, there were differences in evaluation procedures, particularly between the U. K. on the one hand and U. S. and Canada on the other, which were difficult to reconcile in such a way as to obtain comparable data with respect to nutrient supplies. The general problem arose again in 1944 when a "Combined Working Party" representing the U. K., U. S.,

UNRRA and SHANF (Supreme Headquarters Allied Expeditionary Forces) was set up to evaluate the food supplies of the various countries of Continental Europe. The same problem had to be faced later in devising procedures for evaluating the food supplies for the Far East.

The questions here involved might now be dismissed of being of minor importance since the war is over, were it not for two considerations. In the first place, the United Nations Food and Agriculture Organization (FAO) must continue to face these problems. The need for their solution was voiced in the recommendation of the Quebec Conference that "early attention be given to the establishment of a common scientific basis for the determination and expression of nutritive values of foods which will be fundamentally comparable as set forth in the food composition data of different countries, for the improvement of the techniques of food assay, and for the determination of further and more reliable data on the nutrient composition of the world's food supply." In the second place, there are basic scientific questions involved, the solution of which is important for the advancement of nutrition science.

¹ Food Consumption Levels in the U. S., Canada and the United Kingdom. Report of a special Joint Committee set up by the Combined Food Board, USDA, War Food Administration, April 1944, Dec., 1944.

and practice in the various individual countries, including our own

A major problem arises in connection with procedures for calculating the caloric values of foods and diets. In a recent article (1) I have discussed this problem with particular reference to the differences between the U S and U K procedures. In reviewing the experimental basis for Atwater's factors, 4-9-4, and their applicability, it seems to have been forgotten by many that these factors, were calculated to be applicable to the average mixed U S A diet and not to individual foods, nor to mixed diets markedly different in character from one on which the original calculation was based. The upsetting variables here are differences in gross calories among nutrients classed together, such as sugar and starch, and differences in digestibility of a given nutrient according to its source.

Applying Atwater's average factors to individual foods, as is done in figuring calories in tables of food composition, involves no significant error, if these individual food values are in turn to be used in arriving at the overall value of a mixed diet such as is customarily consumed in this country. This is true because the make up of our average mixed diet has not changed since Atwater's time in ways that would call for a modification of his factors, 4-9-4. They frequently give a distorted picture, however, in comparisons of individual foods. Applying them to experimental diets restricted to a few individual foods can also result in a substantial error. For example, consider the data in the following table in which, for simplicity, the calories are calculated on a dry matter basis.

	DIET A	DIET B
Casein	18	18
Lard	15	15
Salt mixture	4	4
Starch	63	
Sucrose		63
Cal. calculated by 4-9-4	459	459
Cal. calculated by factors for individual constituents	468	447

Using the average factors, 4-9-4, the substitution of sucrose for starch doesn't change the calculated caloric value of the diet. But actually, of course, sucrose has a lower value than starch, as Atwater's basic individual values showed. He would have used his individual factors to calculate the values for these two diets, obtaining the data in the last line which reveal a 5 per cent difference.

Further, when one makes up experimental diets, whether of purified nutrients or of natural foods and uses the factors 4-9-4 to calculate their caloric value, he is assuming that they have the

same digestibility for the species in question as is the case for the average mixed diet of natural foods for man—an assumption that may be far from true in some cases. It does seem worthwhile to recognize that these possible errors in the use of the factors 4-9-4 exist, in order to take account of them when the nature of the experiment makes it important. Obviously, the errors can be eliminated by actually determining the digestible calories.

It is in connection with the application of the Atwater factors, 4-9-4, to the diets of other countries which have widely different food patterns that more troublesome errors can arise. Diets which consist more largely of foods of plant origin, and particularly, of less refined cereals as were (and still are), the European wartime diets are overvalued by the Atwater factors. In the consumption-levels studies previously referred to, it became apparent that this was true in the case of the diet of the United Kingdom with its large proportion of 85 per cent extracted flour and potatoes, and its smaller proportion of animal products. A greater discrepancy became evident in the case of some of the continental diets. The table below illustrates how widely the diets of other countries may differ from the U S diet on which the Atwater factors are based.

Approximate Percentage of Total Calories* Supplied by Specific Food Groups

	U S ¹ (1944)	HOLLAND ² (1944)	CHINA (PREWAR)
Milk, meat, eggs and fish	31	16	4.5
Fats and oils	14	9	6
Cereals	28	38	70
Potatoes	4	23	6
Pulses	3	1	11.5
Vegetables and fruits	7	3	1.5
Sugar	13	10	0.5

¹ Second consumption levels report

Combined Working Party Data

² Condensed from Buck's data

Clearly the average factors, 4-9-4 which are based on a mixed diet such as that shown for the U S should not be applied to the food supplies of Belgium and China without a careful consideration of their suitability for the purpose. Actually, they would overvalue the caloric content of both the latter countries, the extent depending on the milling rate for the cereals. For example, the caloric value of polished rice of average composition is 351, but the true values for undermilled and brown rice are approximately 340 and 320 respectively on the basis of their lower digestibility.

The Combined Working Party faced questions of this kind for all countries of Europe and, in view of the time factor, had to solve them by what Sir Jack Drummond referred to as "rough and

ready methods." Procedures by which the basic data of Atwater could be applied to such data have been suggested by the author in the review article previously mentioned.

The difference in the procedures used in calculating carbohydrate calories, by the U. S. and the U. K. scientists, proved particularly troublesome in trying to arrive at comparable data in the consumption-level studies, and also in setting up a standard procedure for both countries to use in evaluating continental food supplies. Here I refer to the "available carbohydrates" represented by the directly determined starch, dextrin and sugar in U. K. food tables, in contrast to "total carbohydrates by difference" in our tables. In the case of certain pulses, potatoes and other vegetables the difference is a substantial one such that the calculated caloric values of the total diet may differ from 3 to 5 per cent according to the carbohydrate basis used. In the case of potatoes which make up 20 to 30 per cent of calories of certain continental diets the difference is of the order of 15 per cent—a difference which does not seem to be borne out physiologically by digestion data. Here lies the specific question which needs further study, as to whether the U. K. "available carbohydrate" actually includes all of the carbohydrate fraction that is digestible and thus useful to the body. While a chemically determined value is obviously to be preferred to one arrived at by difference, proof is needed that a more accurate physiological evaluation is thus obtained, and that the difference involved is a significant one, particularly in view of the extra work entailed. There is the further question, as discussed in the review by the writer, as to the appropriate factor to use in converting "available carbohydrates" into calories.

The foregoing discussion serves to emphasize the fact that the term "available" is not always used to mean the same thing. The calories obtained by Atwater's factors are calories available for metabolism (metabolizable energy) as a result of the deduction of digestion losses and the non-metabolizable fraction of the gross energy of the absorbed protein. "Available" carbohydrates, according to the U. K. definition, are carbohydrates which are capable of being digested and utilized and thus are still subject to possible digestion losses. In a recent review Keys (2) has discussed the term "availability" in relation to metabolic losses. McCance and Widdowson have recently suggested that no attempt should be made to evaluate digestion losses, because of the variability involved, and that the calorie content of foods should be calculated on the basis of the gross factors 4.1, 9.3 and 4.2 for protein, fat and available carbohydrate (as starch) respectively. It is not the purpose of this paper to discuss

critically these various ideas, but rather to record them as problems involved in arriving at any uniform procedure.

The methods used in the U. S. and the U. K. for calculating and expressing the vitamin A values of foods differ so greatly that no satisfactory common basis could be found, in the consumption levels studies, for comparing the supplies of this nutrient in the diets of the two countries. According to the U. S. procedure, as followed in the tables recently issued jointly by the U. S. D. A. and the National Research Council, carotene values are converted into International Units on the basis that one I. U. of vitamin A equals 0.6 ug of B carotene or 1.2 ug. of other vitamin A-active carotinoids. According to the U. K. evaluation, on the other hand, it is stipulated that one I. U. of vitamin A should be considered equal to 1.8 ug. of B carotene. Thus, it is stated that "in calculating the vitamin A potency of a mixed diet the total carotene value should be divided by three and added to the value for preformed vitamin A." That such a procedure would give a much lower value for the same food supply than does the U. S. method is obvious.

While the question of the physiological equivalence of preformed vitamin A and its precursors will continue to be a troublesome one, the principal question at issue in the U. S. and U. K. procedures is as to whether, when carotene and the vitamin itself are combined for expression as a single value, the official international definition that one I. U. of vitamin A is equivalent to 0.6 ug. of B carotene should be adhered to. Agreement here is essential for international comparisons. This situation with respect to vitamin A illustrates the fact that when one is comparing the nutrient content of foods or diets in different countries he needs to satisfy himself that the values are expressed on a comparable basis.

The selection of a dietary which can serve as a yardstick in international comparisons is a problem which is obviously directly related to that of uniform procedures of food evaluation. Such a need was expressed by the Quebec Conference of F. A. O. as follows: Early attention should be given to reassessment of the physiological bases of nutrition in the light of the latest scientific research and wartime experience to provide tables of dietary requirements for use by all countries in terms of nutrients ingested. In the consumption-levels study, the recommended dietary allowances were used, along with a reduced standard as an alternative basis of comparison. Whether a standard which represents a goal and includes rather large margins of safety, or one representing more nearly actual average requirements and to which factors of safety can be added is preferable, involves many considerations concerning which

there are differences of opinion at the present time. A very recent review (3) suggests that multiple dietary standards may be needed, in view of the different purposes to be served. Probably the most important consideration of all is to have a common understanding as to what the standard selected actually means and how it should be used in interpreting food supply data. The misuse which has been made of the R D A well illustrates this point.

The interrelations between methods of food evaluation and the values selected for the standard are obviously close where the evaluation is made in terms of physiological measures. This is illustrated by the U S practice with respect to vitamin A. While it adheres to the officially defined relation between the preformed vitamin and carotene it recognizes that a unit of carotene is less potent physiologically and places the allowance high enough to take account of this

difference, assuming that in a mixed diet two-thirds of the vitamin value will be supplied by carotene.

In this talk I have given examples of problems that have arisen in international food comparisons, rather than making any attempt to survey the entire field. I have called attention to some limitations in our routine methods of food evaluation which need to be recognized, although commonly they may have no practical significance. Irrespective of international applications some of these routine procedures need further research from the standpoint of their technical accuracy in measuring the physiological values which they are intended to portray. In addition, as a service to the United Nations Food and Agriculture program, attention needs to be given to the standardization and unification of procedures on an international basis.

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NUTRITIONAL ASPECTS OF THE MILK SUPPLY

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It is not my intention monotonously to relate the deliberations and actions of the Committee on Milk of the Food and Nutrition Board. It would seem to be more appropriate to attempt to correlate the problems and actions of the Committee with any advances that might have been made toward a better understanding of nutritional needs and to improvement of nutritional status.

At the outset may I emphasize that the Committee on Milk has never felt omnipotent in its knowledge and wisdom and that it drew freely from the vast storehouse of information possessed by other individuals and committees of the Board of the National Research Council, of government agencies, of various scientific societies, and of industry.

The obvious beginning of the job for a committee of this kind was to examine the milk supply and how it was being utilized. Such an examination soon revealed that large quantities of valuable milk nutrients (protein, calcium, riboflavin, and lactose) were not being directed into human food channels. This amounted to a potential annual supply of almost 40 billion pounds of skim milk, 2

billion pounds of buttermilk, and 2 billion pounds of whey. This is the equivalent of a little more than 5 billion pounds of dry powder. Peak production of skim milk, buttermilk, and whey powder was only 750 million pounds (1942). When it was realized that even whey contains 77 per cent of the riboflavin, 26 per cent of the calcium, 32 per cent of the protein, and 97 per cent of the lactose in the original whole milk, it is easy to understand why many nutritional eyebrows more than fleetingly fluttered.

A critical examination of the nutritional contributions made by milk and its various fractions permitted establishment of a three point premise: a) that milk contributes from small to appreciable amounts of all the essential food nutrients and because of this serves as the best food around which to build a complete diet, b) that in evaluating milk as a food at least as much emphasis should be placed on the non fat portion as on the fat, and c) that more of the total solids of milk needed to be directed into human consumption channels.

It was realized that many difficulties, including

those that might be included under the term "pride and prejudice," would be encountered in any program that might extol the virtues of skim milk. As an example let me quote an interesting and amusing observation made 30 years ago by one of my present colleagues (A. E. Perkins):

"Let a piece of the most tempting beefsteak be extracted with water or pressed to obtain broth or meat juice for an invalid, and the solid portion which remains, containing probably more than 95 per cent of the real food material present in the original meat, would be spurned by people as quickly as skimmilk and for the same reason.

"In many cases people, guided mainly by appetite, think they are buying food with more or less flavor thrown in when they are in reality buying flavor with a little food value incidentally included. In the choice of natural foods, appetite is usually a fairly reliable guide to the selection of proper diet, but in these days of sophisticated and modified foods, appetite alone will frequently lead one to spend his living on mere flavored husks, while the real food value of the article, shorn of its flavor, is allowed to waste. It would be difficult indeed to overestimate the effect of these tendencies on the high cost of living."

It became apparent, as demands increased, that milk production needed to be increased and maintained at a high level, that skimmilk needed to be diverted from use on farms for livestock feeding to human use channels, and that emphasis needed to be placed on the production and marketing of those dairy products which would bring about more effective and equitable distribution of the nutrients of milk. Recommendations were made and passed on. From that point on the *modus operandi* was involved, often obscure, and usually unpopular.

We are now in a position to discuss the milk supply and the contribution it can make toward meeting nutritional needs, if the supply is utilized properly. An annual milk supply of 120 billion pounds (the goal for 1946), if completely utilized, would satisfy the vitamin A needs of 45 million people, the protein needs of 67 million people, the riboflavin needs of 130 million people, and the calcium needs of 165 million people. That the milk supply is not completely utilized has already been suggested by reference to the large quantities of skimmilk, buttermilk, and whey remaining on farms. To the extent that these can be fed to calves, hogs, and poultry with economy and efficiency, the disappearance of such milk on farms is justified. Undoubtedly considerable of this reservoir of valuable food nutrients could be used more effectively.

In recognition of this it was suggested that some diversion from cream to milk production, with

proper inducements, might bring a surprising amount of milk into effective human use channels from those areas where livestock feeding operations would not be jeopardized. The inducements were made and what happened?

From 1931 to 1940 there was a moderate, gradual increase in production and consumption of non-fat milk solids. This increase amounted to 9 billion pounds, milk equivalent basis. During the next five years the increase amounted to 18 billion pounds, about half of which was due to a 25 per cent increase in consumption of fluid milk and cream. Whole milk manufactured products, particularly evaporated milk and American Cheddar cheese, increased about 30 per cent during this same period, and the production of non-fat dry milk solids almost doubled. The end result has been that where as previous to the war slightly less than half of the non-fat milk solids produced were used for human food, well over 60 per cent are now being so utilized. This all occurred while milk production increased only 5 per cent and butter production dropped about 20 per cent. Whereas during the period 1932-41 12.3 per cent of the fat solids for civilian consumption came from fluid milk and cream, 13.0 per cent from butter, and 11.7 per cent from manufactured whole milk products, the respective percentages in 1941 were 47.1, 31.0 and 21.6.

Wartime shifts in milk utilization might better be visualized in terms of our principal dairy products. The supply of butter available in 1945 was 80 per cent of pre-war but per capita civilian consumption was only 11 pounds or 33½ per cent below pre-war. To get back to a pre-war level of butter consumption will require that almost 15 billion pounds of milk be diverted from other uses. The supply of cheese available for all purposes in 1945 was 51 per cent above pre-war and resulted from the diversion of 3 to 4½ billion pounds of milk annually from butter making or from increased production.

The annual supply of evaporated and condensed milk increased 88 per cent from pre-war to 1945 but per capita consumption increased only 10 per cent. This is a reflection of the effect of limitations and rationing and probably is not a true measure of the increased demand.

Total civilian consumption of fluid milk and cream increased 20 per cent from pre-war to 1945 and per capita consumption gained 32 per cent during the same period. This increase has required about 13 billion pounds of whole milk, which is about the amount by which milk production increased during the war.

At this point it might be well to indicate the changes that occurred in our nutritional status as we passed through a period of restrictions, regulations, limitations, dietary pattern changes, and substitutions. Not only was the estimated nutritive value of the civilian food supply in 1945

superior with respect to every nutrient to that of the 1935-39 food supply, but the average per capita supply of the various food nutrients exceeded the Recommended Dietary Allowances of the Food and Nutrition Board in every item.

The nutrient content of the food purchased and used by civilians in 1945 was higher than that in 1935-39 by the following percentages: protein 14, calcium 22, iron 28, vitamin A 24, ascorbic acid 22, thiamine 46, riboflavin 39, and niacin 40. Consumption of skim milk products, such as cottage cheese, chocolate drinks and buttermilk was at a record level.

Even without proof, it might not be presumptuous to say that this improvement was due to increased use of all the solids of milk, bread and flour enrichment, and greater use of yellow and leafy green vegetables and of citrus fruits and tomatoes, as well as of meat and eggs. These changes were, of course, made possible because of increased incomes, rationing, nutrition education and manipulation of the agricultural program.

Unfortunately, however, values such as those just given are obtained by dividing the total civilian population into the total civilian food supply and assuming equitable distribution. That equitable distribution does not occur is well known and it is there that the great opportunity lies in fortification of certain food staples and in extending the use of milk solids in the form of evaporated milk, whole and non-fat dry milk solids and cheese into the low income segments of our population and into those geographical areas where the fluid milk supply is inadequate. Coincident with this should go a dairy industry development program in areas that have been traditionally non-dairy in character but for which no real inherent obstacle exists.

Were I to select recommendations of the Committee on Milk that might have the most far-reaching effect it would be those concerned with the advantages to be derived from including milk in commercial and home prepared bakery products. I would cite particularly the one calling attention to the need for developing at the earliest practicable moment a program for placing whole and non-fat dry milk solids at reasonable cost and in amounts convenient for use in the home within the reach of consumers, especially in areas where fluid milk consumption is low. This suggested program might constitute a challenge for post-war activity by all groups interested in improving the general public welfare. That this does constitute a challenge is indicated by the results of a recent study in Houston, Texas, covering the period January 1944 to April 1945. In spite of the fact that promotion was conducted through radio and newspaper advertising, through test-kitchen demonstrations, and through use in school lunches, railroad section gangs, boarding houses, and drug

stores, the conclusion was reached that "consumer acceptance of dry milk has been neither an unqualified success nor an unqualified failure." The test-kitchen method was found to result in the greatest response and whole milk powder was chosen much more frequently than skim milk powder. Of interest, too, was the opinion of some grocers that people have little need for non-fat solids. This statement is presumed to have been based on the popular idea that all the food value of milk is contained in the fat.

In late 1942 and early 1943 milk rationing on a coupon basis was seriously considered. This resulted in the preparation of a guide to milk rationing in which an attempt was made to allocate daily allowances of milk for various population groups. You will be interested to know that even with the shortest prospective civilian supply allocation could have been made to provide milk in all forms to the equivalent of 7 quarts per week for pregnant women, and children under one year, 5.0 quarts per week to children 1 to 11 years of age, 6.0 quarts per week to children 12 to 18 years of age, and 2.5 quarts per week to other persons. Increased production and further diversion were advocated, however, and milk never was rationed except on a voluntary basis to a limited extent.

Sugar was rather bitter at times but in a preference rating ice cream, sweetened condensed milk, sherbets and ices yielded to bread, breakfast cereals, prepared flour mixes, commercially packed fruits, and even to cakes, cookies, jams, and jellies.

In 1943, production of adequate quantities of penicillin became critical. This naturally led to a priority listing of lactose uses and to recommendations regarding lactose production. We all know that penicillin became available in abundance, but two side lights may be of interest. First, use of lactose in prepared infant foods was considered essential, second to illustrate the wide scope of counsel employed on occasion, three committees of the National Research Council, four divisions and branches of the War Food Administration, one Bureau of the Agricultural Research Administration, one division of the Food and Drug Administration, one Bureau of the War Production Board, the American Pharmaceutical Association and National Formulary Committee and the U. S. Pharmacopoeial XII Committee on Revision were involved.

Considerable attention was given to the matter of milk fortification. General fortification of milk with minerals or with vitamins other than vitamin D was not favored. Nor was allocation of ascorbic acid for fortification of the general production of evaporated milk. Allocation of ascorbic acid for addition to evaporated milk intended to help meet the ascorbic acid needs of special and selected groups was advocated, as was the addition of ascorbic acid to special infant foods with a milk base.

But enough of this braggadocio or confession!

As academic attempts or accomplishments one can turn to the recently completed national survey on the vitamin A potency of butter produced in the United States. Originating with a suggestion from the Food and Nutrition Board, this study mushroomed, under the guidance of the U. S. Bureau of Dairying and the Office of Experiment Stations, into a nationwide cooperative study in which 19 experiment stations and the Beltsville Research Center participated. The outcome was the discovery that butter is a much better source of vitamin A activity than previously supposed (the weighted national average potency is 15,000 I.U. per pound), that little vitamin A activity is lost from butter stored for as long as a year, and that by improved forage harvesting practices and better winter feeding of our dairy cows the vitamin A activity of butter can be increased still further and be made seasonally more uniform.

The unfinished symphony of the Committee is a comprehensive monograph, now in the process of preparation, on the nutritive value of skim milk. This is intended to be a reference source of information for professional groups, from which a popularized version will emanate for wide distribution.

It is time now to consider what the impact of all this may be on our future efforts and well-being. Consumption of fluid milk at a high level can be maintained in the post-war period by a full employment program that will insure adequate incomes. In addition, the use of milk in schools and as part of industrial in-plant feeding will need to be developed far beyond the pre-war stage. I like the way Dr. J. C. Drummond of England expressed these thoughts in an address before the Royal Society of Arts at the height of the war:

"There is everything to be said for distributing more equitably such supplies (of milk) as were available. By one way or another this has been achieved. The Milk in Schools Scheme, the Special Category Priority Scheme, The National Milk Scheme, each has served to flatten out the steep consumption-income curve of pre-war years. This naturally has raised a few grumbles from those who were fortunate enough before restrictions were imposed to be able to purchase all they wished to have, but we regard their troubles as trivial when we look at the benefits gained by the poorer people who have thus been enabled to get a fairer share of a food that has been aptly described as the keystone of the nutritional structure.

"If we look to the post-war years, we cannot see ourselves reverting to a state in which the consumption of milk can be seriously restricted by lack of purchasing power.

"The consumption of milk in one form or another must be raised. Our post-war target should be a level 100 per cent higher than the present figure—which, it may surprise you to learn, are actually higher than in 1939. But the curve must not be allowed to become steep again. Nearly a horizontal line, as it now is, its level must be raised without changing its shape. I believe that will be done. If it is, it will be a direct outcome of our nutrition policy during the present war.

That the situation in the United States is similar to that described by Dr. Drummond is apparent from two studies made by the Bureau of Labor Statistics. A study made in 1942 showed that per capita purchases and expenditures for dairy products increased with increases in family income levels, except for evaporated milk, where purchases and expenditures per capita tended to decline as family income increased. A similar study, made in 1944, showed that purchases of dairy products by families with income levels above \$2,000 were restricted materially when compared with the 1942 study. The effect of rationing, particularly of butter and cheese, resulted in a leveling out of purchases per person at various levels of family income. Purchases of these two commodities were about the same in families with over \$4,000 net income as in those with incomes under \$1,000. In the case of fluid milk, however, where the restrictions were less severe, the consumption pattern in the fall of 1944 was about the same as in the spring of 1942.

When we speak of raising the milk consumption level, we mean milk in all its forms. In the field of dried milks, for example, a post-war human utilization of about a billion pounds is visualized for such uses as in the baking industry, in institutions, in confectionery and chocolate making, in the armed forces, in ice cream in households, in sausage, soups and cereals, in milk drinks, in margarine manufacture, and for direct distribution and export.

To accomplish this, however, will require the cooperation and concerted efforts of government, education, science, and industry. One of the greatest fields of activity will be that of research—the kind that starts with the soil and carries through the production, processing, and marketing stages, for our most recent research points out the interrelationships between production practices, nutritive value, processing characteristics, marketability, and consumer acceptance. The incentive will be the knowledge that more equitable distribution of the vital food materials found in milk can do much toward improving the standard of living of the masses and help conserve the world's greatest natural resource, which is its people.

HUMAN DIETARY ALLOWANCES

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The most recent summary of the needs of humans for the various nutritional essentials was that of the Food and Nutrition Board of the National Research Council. This Board was organized late in 1940 in preparation for what appeared to be an impending national emergency. The goal was to consider the scientific aspects of nutrition in relation to the general program of national defense and to do whatever seemed indicated to improve the nutritional status of our people. As a starting point it was necessary to know in some detail the nutritional needs in terms of the nutritional essentials. Food planning would be impossible without some kind of a standard. Both military and civilian needs were to be met. It was necessary to have a guide for the purchase and distribution of food for the armed forces and as to the amounts needed for lend lease. It was advantageous to have a guide as to what is desirable in food allowances for population groups. As a corollary to these needs it was advisable to have a guide as to the quantity of food stuffs needed to be grown and produced. If food supplies were to be assessed and planned, a standard became essential. The creation of such a standard became one of the early primary objectives of the Board.

The type of standard needed was not in existence. In 1935 and 1936 the Technical Commission of the Health Committee of the League of Nations published a report on the physiological bases of nutrition in which were set forth nutritional requirements for various age and other categories. Except for calories and protein, these requirements were chiefly in terms of foodstuffs rather than in terms of specific essentials. Furthermore, the more recent advances in nutritional knowledge were not represented. For the purposes of the Food and Nutrition Board it seemed preferable to formulate the standards in terms of specific essentials which then could be translated to food stuffs available in different localities.

Based on public hearings that had been held the Food and Drug Administration had set up standards for regulatory purposes. These standards included most of the categories finally adopted by the Food and Nutrition Board. However they were intentionally formulated as minimum requirements and it became desirable to have standards that offered something more nutritionally than a bare minimum. The goal desired was optimum nutrition, a condition that cannot be assured with requirements that are minimum for the average person.

A special committee of the Food and Nutrition Board undertook to assess the literature and the results of current research. The tentative allowances thus estimated were submitted to numerous consultants qualified by research and experience to express opinions. Values were derived that met the approval of the majority of the consultants and of the Board. The values were then submitted to the National Nutrition Conference for Defense in May 1941, they were approved by this conference. A few additions were made in 1942. The allowances were published as Bulletin 115 of the Reprint and Circular Series of the National Council. By 1944 research results indicated that the allowances for the B vitamins were overgenerous in some categories. After many months of consideration of the evidence and particularly after consultation with persons engaged actively in research with the B vitamins, the revision of 1945 was approved and released.

In the 1945 revision allowances were included for several factors in addition to the essentials listed in the older table, but the chief change consisted of downward revision of the values for the B vitamins at levels of calorie intakes above 3000. The revised allowances were published as Bulletin 122 of the Reprint and Circular Series of the National Research Council, a publication that included an explanation of the means by which the values of the allowances were derived. The values of the 1945 revision represented the best group judgments that could be obtained. In some instances individual opinions differed from those of the group, but the table represents majority opinions of a rather large number of qualified persons.

Those responsible for the table are fully aware of its weaknesses. In some categories values were lacking and had to be interpolated. Particularly is this true for adolescence. Adolescence is a period of increased metabolic stress and the nutritional needs are greater than those of other periods. However, few data have been published for this period. While we have much nutritional knowledge and that knowledge is constantly increasing, no one or no group has enough to assign accurate and final values in a table such as that of the Allowances for any given essential. It is amazing how few standards could be laid down with any degree of uniformity of opinion notwithstanding what appears to be a large amount of research. Yet the military forces had to be fed and long range plans were necessary. The

formulation of reasonable standards became imperative despite the known difficulties.

The setting up of standards for calories, protein and the minerals presented fewer difficulties than for the vitamins, chiefly because knowledge concerning the former was older and had been accumulating for a longer time. There existed more data on which judgments could be based and the existing data presented relatively few conflicts. On the other hand determination of the vitamin allowances required much more discussion and often some degree of compromise among the various investigators.

The greatest difficulty was encountered with the thiamine allowances. In addition to assessing the published data, a conference was held with a group of persons engaged actively in research with the human requirement for thiamine. Extreme views were represented and the minimum requirement advocated ranged from 0.23 mg. to 0.35 mg. for each 1000 calories. When experts differ, attainment of a consensus of informed opinion is difficult. However, the goal of the committee was a safe allowance without undue excess. The committee was not concerned primarily with minimum requirement. With little exception those supporting a low minimum requirement were willing to agree to a higher value as an appropriate allowance to be recommended. It was finally agreed that a suitable allowance would be 0.5 mg. for each 1000 calories up to 3000 calories and 0.3 mg. for each 1000 calories above 3000. These values were approved by most of the consultants and of the members of the Food and Nutrition Board. Continuing to relate the requirement to calories seemed good practical usage even though the same relationship does not hold at all levels of caloric intake. By this means the same ratio is applicable in all age categories.

Evidence for the riboflavin requirement for humans is meager. The amounts recommended by the Board were influenced by the recorded human experiments as well as by observations with animals. The animal experiments indicated that the riboflavin requirement is related to that for thiamine. The human experiments were made with adults. For other age categories the relationship to thiamine was the chief guide. Obviously more experimental data are needed.

Knowledge of the nicotinic acid requirement is in an unsatisfactory state in that few experimental data are available for humans. The allowances recommended were influenced greatly by the observation that a relationship between the niacin and the thiamine requirements exists in dogs, the same ratio was retained in formulating the allowances. Maintenance of this ratio probably allows for minimum need, inasmuch as

possible synthesis with a generous supply of milk in the diet is not allowed for. Also the relationship of the nicotinic acid need to the amount of tryptophane in the diet remains to be clarified.

Knowledge of the ascorbic acid requirement is in a more satisfactory state than that for any other vitamin. Even so a few problems still exist, such as decision as to the appropriate blood level or as to the amount excreted in the urine as a criterion of satisfactory stores.

The vitamin A values of the table are based chiefly on results of dark adaptation experiments. Dark adaptation procedures have been subject to much criticism, at least some of which is believed to be unjustified. The best alternative criterion would be blood values, but studies of blood values have not been conducted in such a manner as to offer criteria for determination of the requirement. The anatomical lesions of vitamin A deficiency are not easily usable for determining the requirement. The official minimum values of the Food and Drug Administration also were based on dark adaptation experiments. Regardless of the fallibility of their derivation, the vitamin A values recommended are supported by collateral evidence of animal experiments. It is to be pointed out that a rather wide diversity of judgment exists as to the appropriate values for vitamin A. However, the values of the table are believed to be generous allowances. They are easily attained with any good diet.

The preceding discussion of vitamin A refers only to adults. Almost no data exist for children. It has been customary to consider the vitamin A requirement as proportionate to body weight. If the allowances for adults were apportioned for children in relation to body weight, the amounts would be less than those that have been assigned. To obtain the assigned values a factor was used similar to the one known to be necessary for protein. In order to state the protein requirement in terms of progressive body weight, a series of decreasing values is used, beginning at 3.5 grams for each kilogram in infancy and decreasing gradually to the 1 gram value for adults. The use of such a factor for vitamin A was arbitrary, yet it gave values that experienced nutrition workers were willing to accept as reasonable and satisfactory. Obviously much study of the vitamin A requirement of children is needed.

In judging the appropriate amount of vitamin D for infants we find some conflict between the interpretations of clinical experience in large scale outpatient studies and interpretations of both clinical and balance studies of smaller but better controlled groups. The latter type of study gives results indicating that 300 to 400 units daily is a fully adequate amount for infants. At this level of intake linear growth of infants exceeds the

average in rate, retentions of calcium and phosphorus are excellent, dentition occurs earlier than average. Any amounts of vitamin D greater than 300 to 400 units daily do not increase the calcium and phosphorus retentions above those observed with this lesser amount. Yet some confusion has arisen because of criteria used in interpretation of roentgenograms by a few observers. On the basis of the structure of the metaphysis of the long bones the diagnosis of rickets has been made in the case of infants receiving 300 to 400 units of vitamin D. Naturally, if rickets occurs with this amount of vitamin D, a larger amount is indicated. However, these bone changes do not occur with 135 units of vitamin D, a much smaller amount and one that produces smaller retention of calcium and phosphorus. A more appropriate interpretation is that the bone changes observed with 400 units are definitely not rachitic and probably are concomitants of the rapid growth that occurs with this intake. It was because of this conflict of opinion that the range of 400 to 800 units was stated in the table of allowances.

The vitamin D requirement beyond infancy is known with less certainty than that for infants, but the values in the table of allowances are believed to be ample. Children beyond infancy who are receiving 300 to 400 units of vitamin D daily have retentions of calcium that correspond to the normal as determined by calculations based on rates of growth.

The calcium allowance for adult males is well based on experimental evidence as is also that for children of the preschool age. Some, but insufficient, evidence exists as to the needs of adolescent girls. For other values during the growth period interpolation was necessary, though the more recently published values of Macy give support to the interpolated values. The exact values appropriate for pregnancy and lactation have not been determined, though it is certain that an increase of the general order stated in the allowances is necessary for calcium equilibrium. The most important lack of evidence of the calcium requirement exists for the adolescent period.

In the preceding discussion I have indicated the mechanism of the formulation of the allowances and have pointed out some of the deficiencies of our knowledge of human requirements for the nutritional essentials. I am sure that I speak for the Committee on allowances and the Food and Nutrition Board when I say that constructive criticism will be welcomed and that all facts submitted will be given full consideration.

In the endeavor to bring national nutrition to the desirable levels of the allowances, the Food and Nutrition Board undertook numerous other activities as has been discussed by other speakers this morning. The Board strongly encouraged the

enrichment of flour and bread, the addition of vitamin D to milk and the fortification of margarine with vitamin A. The Board studied and advised concerning the needs of milk production and the interrelation of the human needs for milk with the protein feed situation for livestock. Most aspects of animal nutrition were in the purview of the advisory committee on feed composition of the Agricultural Board of the National Research Council which was in close liaison with the Food and Nutrition Board. This committee undertook a task comparable to that of the committee on food composition of the Food and Nutrition Board. Also it devised Recommended Nutrient Allowances for farm animals in a manner comparable to the work of the committee on human allowances. Bulletins were published relating to the nutrient allowances for poultry, swine, dairy cattle, beef cattle and sheep. These bulletins could well serve as a basis for studies of comparative nutrition.

The recommended dietary allowances of the Food and Nutrition Board were formulated to be a goal for the nutritional welfare of all normal persons. It is to be emphasized that they do not represent minimum or even average requirements, but rather the amounts of nutritional essentials desirable in the diet. The term average presupposes that some persons require more and some less. The allowances were designed to meet the needs of those normal persons who require somewhat more than the average, those with less efficient usage but still normal. Thus a factor of safety is provided for those who have average or less than average requirements, yet the amounts recommended may permit only maintenance requirements for many normal persons.

It is obvious that the allowances cannot be used as the sole criterion for determining the nutritional status of population groups, many persons are amply nourished and remain in good health, yet receive less of one or another essential than the amounts recommended. However, the allowances can be used as a guide in feeding population groups. In some instances the total food supply may not permit attainment of these standards. In such cases one can take some solace in the fact that the average requirements are less than those recommended. But also one must recognize that the needs of all normal persons are not met by values representing minimum or average requirements. Thus one must distinguish between immediate consumption goals and standards based on good nutrition for all.

The allowances have potentialities for innumerable applications. Throughout the war they served as standards for the diets of our military forces throughout the world. Master menus were prepared with the allowances as a guide. The al

allowances are useful in making dietary surveys, in assessing the needs of our civilian population and as a guide in feeding population groups. They have been widely used as guides for family buying for welfare administration. They have been used as a basis in determining production goals. They serve as a focal point for guiding research that is to fill those gaps in our knowledge which are

evident from a review of the derivation of the allowances. It is my belief that the Recommended Dietary Allowances, despite their recognized imperfections, will stand as a monument to the activities of the Food and Nutrition Board during the war period. Their importance will be even greater if they can be revised from time to time.

THE SIGNIFICANCE AND LIMITATIONS OF FOOD COMPOSITION TABLES

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Eventually it should be possible to determine the nutritional value of any diet through the use of figures for dietary requirements, tables of food composition and a calculating machine. Our hope of attaining this goal rises and falls with each new development in the field of nutrition, but these new developments are now taking place so frequently that final success should not be delayed too long. Some of the problems relating to dietary requirements have been discussed in last year's Symposium on Human Vitamin Requirements (1) in the revised bulletin on dietary allowances (2) and by the previous speakers. I shall try to outline some of the significant problems related to food composition.

Hundreds of papers dealing with the composition of foods have been published but relatively few workers have taken the time and effort to compile these values into comprehensive tables. In 1896 Atwater and Woods (3) published an extensive compilation on the proximate analysis of American food materials. This bulletin has been used as a standard reference and tables in most textbooks are based to a considerable extent on these early values.

In human nutrition the tables prepared by H. C. Sherman have been used most extensively. In the 4th edition of *Chemistry of Food and Nutrition*, 1932, the values for proteins, fats and carbohydrates were based largely on the Atwater-Bryant tables but values for ash constituents were obtained from a critical compilation of all available analyses both American and European. It was in this edition that values were uniformly given as the elements rather than as their oxides. It is also important to mention that average values were used in all cases rather than the maximum and minimum figures given by Atwater and Bryant. In this edition values for vitamins were expressed in + and - signs. In the 6th edition of *Chemistry of Food and Nu-*

trition, the older values were revised in light of more recent information and specific figures were given for the vitamin A, thiamine, riboflavin and ascorbic acid content of food.

Further tabulation has been carried out largely in the Bureau of Home Economics. In 1928 Chatfield and McLaughlin (4) and in 1931 Chatfield and Adams (5) prepared new summary tables on the proximate composition of fresh fruits and vegetables. Chatfield and Adams (6) prepared similar tables for all foods in 1940. Similar tables on the vitamin content of foods have been prepared by Daniel and Munsell (7) and Booher, Hartzler, and Hewston (8).

In the animal field the most extensive summaries have been made by F. B. Morrison in *Feeds and Feeding*. The 20th volume of this book gives proximate composition but no values are given for the vitamin content of feeds.

In the fall of 1942 the Office of the Quartermaster General requested the Food and Nutrition Board to establish a committee to assemble, coordinate and appraise data on food composition for the War Department. A Committee on Food Composition was appointed (membership of the committee is given in the *Journal of the American Dietetic Association* 20, 215, 1944) and one of the first problems undertaken was to compile a table listing proximate, mineral and vitamin values of some 250 foods. The basis for this table was dependent upon values which had been compiled under Miss Chatfield's direction at the Bureau of Home Economics. In addition, a thorough search was made of all reliable data in the literature and later a public request brought in a vast amount of unpublished data from laboratories throughout the country. It was especially helpful that a few extensive research programs such as work on meat and cereals had been underway for some time and many data for these products were immediately available. The organization early in 1942 within

the State agricultural experiment stations and the Department of Agriculture of a National Cooperative Project on the Conservation of the Nutritive Value of Foods also served to focus attention on this problem and this program has been very valuable in making available reliable data. In some cases special research projects were established such as that sponsored jointly by the National Canners Association and the Can Manufacturers Institute. This program made available many figures on canned and dehydrated products. When no data were available or when existing data did not seem consistent, properly selected samples were submitted to the laboratories throughout the United States that were best equipped to make each of the specific determinations. In this connection collaborative assays were set up for some of the vitamins to establish the reliability of the methods used.

To serve the immediate needs of the Army, the Tables of Food Composition were mimeographed and underwent three revisions during the two year period. During these tabulations most information on regularly consumed civilian foods was also accumulated. In order to make best use of this information, printed tables of food composition in terms of 11 nutrients has been published jointly by the Bureau of Human Nutrition and Home Economics and the Food and Nutrition Board. This bulletin is available as U. S. Department of Agriculture Miscellaneous Publication No. 572. Two tables are included, one giving the nutritive value of 100 grams of selected foods, edible portion, and the other the nutritive value of 1 pound of selected foods, as purchased.

What is the value of these, or any similar tables of food composition? If all the foods are listed and values for all nutrients given these tables may be used for calculating the adequacy of any diet, for planning production programs both national and international and for projects established to improve the quality of foods produced and consumed. We must admit that the printed tables do not include all foods now used in the United States and certainly not foods consumed in other parts of the world. However, it is interesting in this connection that similar tables have been prepared by workers in other countries. In England we have "Nutritive Values of War Time Foods" published as Medical Research Council War Memorandum, No. 14. In South Africa we have "South African Food Tables" prepared by Fox and Goldberg and similar tables have been prepared in Canada (9) and Australia (10). The Food and Nutrition Board established a committee on international food value problems which has attempted to correlate data in individual tables for use in international problems. Actually foods may differ from country to country and the methods of handling food gives

us different types of flour, different cuts of meat and milk with a different fat content. A recent paper by Cravitt et al. (11) indicates that the nutritional qualities of the foods of Mexico may be quite different than those of the United States. These are problems which need to be studied by the new Food and Agriculture organization.

However, it is more important that Publication No. 572 omits many prepared foods because of their lack of uniformity. The restored cereals were not included because at the present time no official standards of restoration have been promulgated. In spite of this situation a large proportion of our breakfast cereals are restored cereals. In the extensive program on the composition of canned foods, special or formulated products have been omitted because of lack of uniformity. Again the consumption of some of these special products, especially prepared soups, is very high.

I have already indicated that values are presented for only 11 nutrients. Certainly we must expand this list if we hope to have any degree of completeness. We all agree that values for proteins are only very approximate and sooner or later we must have specific values for each of the essential amino acids and perhaps for all the amino acids. Values for total carbohydrates are given in No. 572 and values for available carbohydrates are given in the British tables. This brings up an important question regarding the calculation of total energy and this has been discussed thoroughly by Maynard (12). However, more important than the energy problem is the fact that different carbohydrate in the diet have different effects on intestinal synthesis of vitamins and perhaps the utilization of various minerals. Some day then, we will want values for each of the different carbohydrates. McCance and Widdowson (13) have determined glucose, fructose, sucrose and the starch and dextrin in a number of foods.

Values are given for only 3 minerals and certainly other mineral elements need to be added such as sodium, potassium, magnesium, copper, iodine, fluorine, manganese and cobalt. Peterson, Skinner and Strong (14) have included figures for copper, manganese, zinc and iodine. In the case of vitamins values are given for 5 vitamins but we need to continue our work to tabulate values for vitamin B₆, pantothenic acid, choline, biotin, folic acid, etc.

What is the accuracy of the values found in these modern food composition tables? I believe most workers are agreed that the reproducibility of results obtained in different laboratories on the same sample by the same method, is excellent for the better known vitamins and minerals. For example, in a recent collaborative assay on a canned pea puree, 18 out of 25 laboratories re-

ported values for thiamine between 0.18 and 0.22 mg/100 grams and 16 out of 21 laboratories reported values for niacin between 1.2 and 1.4 mg/100 gm. Guerrant, Vavich and Fardig (15) have recently compared vitamin values obtained by different methods of assay and conclude that in order to secure results of maximum scientific value in collaborative studies the following conditions should be ensured: "(a) that representative samples of unquestionable uniformity be prepared in quantity from the same initial source, (b) that these samples be stored under the same conditions prior to assay, (c) that stable vitamin reference standards be placed at the disposal of each collaborator, and (d) that each collaborator use the same methods in which all details of procedure and quality of reagents are carefully prescribed." The homogeneity of samples must be given special consideration when dealing with such minute quantities of nutrients as encountered in the case of vitamins. In spite of the rather satisfactory results obtained when these conditions are followed, some of the present methods need modification when applied to certain types of food products.

A more important problem is whether the methods used measure the true biological value of the food as far as each specific nutrient is concerned. The total calcium content of a food high in oxalic acid may not be a true measure of the available calcium. It is well known that all the iron in some foods is not readily utilized. Although several methods for measuring available iron have been developed, there is no clear evidence that these procedures measure the iron which is available to the human. There is undoubtedly a fair correlation but the relationship may not be quantitative. Miller and Louis (16) have recently studied this problem further and conclude that the percentage of food iron soluble in dilute acetic acid or dilute sulfuric acid bears no relationship to the amount of available iron as determined by bioassay.

When the vitamin A potency of most foods is measured, we must contend with both vitamin A and carotene. British workers have attempted to compensate for the reduced activity of carotene directly in Tables of Food Composition. However, it appears better procedure to tabulate the actual amount present and make some allowance for carotene in the figures for dietary requirements.

The values for butter obtained in 14 different states by estimating vitamin A and carotene separately, show remarkably good correlation (17). There is still some controversy over the estimation of ascorbic acid and dehydroascorbic acid since it is difficult to establish the exact biological activity of dehydroascorbic acid. The agreement between the animal assays and the

chemical and microbiological assays for thiamine, riboflavin and niacin is surprisingly good. More work is needed in the case of pyridoxine, pantothenic acid, biotin, etc.

The variation between individual samples of a given food material is much more difficult to deal with. We know that natural variations in the vitamin content of plant foods is affected by the soil in which the plant is grown and the climatic conditions under which it is grown, by varietal differences and by the effect of maturity and by the part of the plant sampled. For example, Jansen (18) has recently reported that the thiamine content of 88 different varieties of potatoes varied from 0.03 to 0.16 mg per 100 gm. or over 500 per cent. However, the average variation was only 22 per cent for potatoes of the same variety grown on the same plot and harvested at the same time. In the case of animal products, the feeding practice may have considerable effect on the composition of the finished animal. Some of these possible errors can be compensated for by subdividing the foods into definitely described groups as to variety, maturity, etc. and by increasing the number of samples analyzed. It should be noted that in Bulletin 572 such distinctions have not been made and any future table should take this matter into consideration.

In reference to the butter samples referred to previously, it is important to point out that about 3500 different samples were analyzed. This may account for the excellent agreement which was obtained. In Tables 1 and 2 comparisons are made between values obtained on typical canned products in two different years, 1942 and 1943 (19). Even in the case of pears in which almost 100 samples were analyzed the average riboflavin content for 1943 is about 10% higher than the average in 1942. In the case of tomato juice which is of more uniform quality, the figures for the 2 years are practically identical. There is also some variation in the niacin content between the two years in spite of the large number of samples analyzed. The largest discrepancy occurs in the case of sardines where only 5 and 6 samples were analyzed. It is interesting that the values for riboflavin and niacin given in Publication 572 fall in between the values for the 1942 and 1943 packs.

Another means of checking the accuracy of Food Composition Tables is to compare the composition of specific meals as obtained by calculation from Food Composition Tables against that obtained by actual analysis. Widdowson and McCance (20) have found that the actual composition of diets is closely approximated by the values obtained through the use of food tables in the case of protein, fat, potassium, magnesium and phosphorus. Greater differences were obtained in the case of calcium and iron. Somewhat similar studies have

been carried out by McHenry and coworkers and again the agreement is fairly satisfactory although in some cases differences as high as 200% were obtained. This work has been summarized in Nutrition Reviews (21).

What are the limitations of the Food Composition Tables? As has already been pointed out the best correlations are obtained when tables are used for calculating the composition of rather large numbers of meals. Thus it would be difficult to use a table of food composition for calculating

beginning to recognize that fresh vegetables preserved in ice directly after harvesting will supply more vitamin C than the average type of vegetables for which the figures are now given. The effect of storage is also a factor even in the case of dehydrated products. Due to a special project sponsored by the Committee on Food Composition it is possible to record in Publication No. 572 values for the more important dehydrated food products. It is evident from Table 3 that it is impossible to estimate even the more stable nutrients by direct calculation from the fresh product. There is, apparently, also a loss of elements

TABLE 1

Riboflavin content of canned food sampled in 1942 and 1943

	1942*			1943**		
	No of sample	Range	Average	No of sample	Range	Average
		mg per 100 gm			mg per 100 gm	
Beans lima green	26	0.023-0.062	0.042	28	0.022-0.053	0.037
Peas sweet	94	0.025-0.100	0.034	57	0.047-0.078	0.061
Spinach	31	0.024-0.130	0.082	25	0.064-0.150	0.110
Tomato juice	79	0.007-0.046	0.025	61	0.017-0.039	0.027

* University of Texas

** University of Wisconsin

TABLE 2

Niacin content of canned foods sampled in 1942 and 1943

	1942			1943		
	No of sample	Range	Average	No of sample	Range	Average
		mg per 100 gm			mg per 100 gm	
Beans lima green	27	0.32-0.77	0.55	6	0.11-0.83	0.48
Peas sweet	94	0.42-2.69	1.06	56	0.55-1.30	0.91
Sardines in oil	5	2.32-7.15	5.67	6	3.4-5.0	4.00
Tomato juice	77	0.55-1.77	0.75	60	0.42-1.0	0.81

TABLE 3

Composition of fresh and dehydrated foods

	DRA MATTER	PROTEIN	CARBO- HYDRATE	CALCIUM	PHOS- PHORUS	VITAMIN A	THIAMINE	RIBO- FLAVIN	NIACIN	VITAMIN C
Cabbage										
	gm	gm	gm	mg	mg	I U	mg	mg	mg	mg
Fresh	7.6	1.4	5.3	46	31	80	0.07	0.06	0.3	52
Dehydrated	91.2	13.7	68.8	374	274	520	0.41	0.37	2.4	169
	12X	10X	13X	8X	9X	6.5X	6X	6X	8X	3.5X
Potatoes										
	gm	gm	gm	mg	mg	I U	mg	mg	mg	mg
Fresh	22.2	2.0	19.1	11	56	20	0.11	0.04	1.2	17
Dehydrated	92.8	7.1	82.0	25	103	0	0.20	0.10	4.8	26
	4.5X	3.5X	4.5X	2X	2X		2X	2.5X	4X	1.5X

the composition of individual meals or meals of atypical composition. While average figures have been used in most of our recent tables it would be valuable to have figures for the maximum and minimum and perhaps figures which fall within a certain narrow range of values. Such values would be especially important when we are interested in specific foods as sources of specific nutrients. Sherman has emphasized the fact that cabbage grown in home gardens and consumed directly supply more vitamin C to the American dietary than cabbage grown on a large scale and distributed through the regular channels. We are also

such as calcium and phosphorus during the dehydration process.

There may be a considerable loss of nutrients such as thiamine, ascorbic acid, and carotene during the storage of dehydrated products especially at elevated temperatures. Heberlein and Chifcorn (22) have shown that the beneficial effect of inert gas packaging on the preservation of carotene and ascorbic acid in dehydrated fruits and vegetables is overshadowed by losses due to elevated temperatures of storage. Thiamine is most susceptible to destruction unless the moisture content is reduced to less than 2%. For example, in dehydrated

meat (23) most of the thiamine was stable at 10° F but at 70° F there was a definite loss after 30 days, and a large loss after 12 weeks. At 100° and 120° F the loss was apparent after one week and almost complete after 10 weeks of storage. Thus, a specific batch of dehydrated pork stored for 10 weeks at 100° F would be of little value as a source of thiamine even if the original product showed a value of 1.4 mg per 100 grams.

Furthermore, the values given in the table do not allow for cooking losses. It is important to emphasize that the losses due to processing in the kitchen are not as great as some workers have suggested if a reasonable amount of care is taken.

TABLE 4
Retention of vitamins in large scale cooking

	PER CENT RETENTION			
	Thia mine	Ribo flavin	Niacin	Ascor bic acid
Meat	65	80	75	
Meat plus drippings	75	95	90	
Eggs	75	80	75	
Cereals	90	(100)	90	
Legume	(100)	(100)	(100)	
Leafy green and yellow veg. tables	60	75	75	40
Tomatoes	95	95	95	85
Other vegetables	75	85	75	40
Potatoes	60	75	75	40

In an extensive study by Flynn and Hogan (24) the total over-all loss in several meals was 10% for vitamin A and thiamine, none for riboflavin, 13% for niacin, 23% for ascorbic acid and 13% for ash. One-half of the fat was lost or discarded from the food before it was finally served. Similar results have been reported by McCay (25) in studies on Navy rations.

In order to determine the exact losses due to cooking we have the problem of how to calculate the amount of loss. The loss may be calculated on the basis of dry weight in the original and in the cooked food or by the per batch method. The experience of the Committee on Food Composition indicates that the latter method is the most pref-

erable. In some cases, at least, the losses due to cooking are different on the small scale and large scale procedures.

Table 4 gives a very preliminary summary of the retention of nutrients during institutional cooking. In the future we may have tables which will show the composition of raw foods and the same foods after cooking. In fact, the Yardstick, prepared by the National Livestock and Meat Board includes values of this kind. However, at present the Committee on Food Composition hopes to supplement the tables given in Publication No. 572 with values showing the average retention during average cooking procedures.

Finally we must not overlook the fact that there are still many factors which cannot be measured quantitatively and therefore, do not appear in the Tables of Food Composition. There are still new factors to be isolated and naturally no figures for these factors appear. Thus, one of the dangers resulting from the use of Tables of Food Composition is that if a diet meets the recommended dietary allowances as calculated from these tables it is assumed that the diet is optimum. One of the best examples of such a limitation relates to the incidence of dental caries. There are undoubtedly, many factors involved in the prevention of caries which are not measured by the recognized quantitative methods. However, it should theoretically be possible to extend the number of columns in a table as more information is obtained and at some later date we should have sufficient columns to take care of all of the necessary nutrients.

In conclusion, I think it is important to emphasize that although we have added many foods and several nutrients, we have the same problems today which Atwater (26) recognized 50 years ago. In U S D A Bulletin 21, Atwater made the following statement: "Investigation is especially needed in two directions (1) the study of the methods of analyses with a view to their improvement and (2) analyses of a sufficient number of specimens to give a clear idea of the range in composition and the average proportion of ingredients in the materials in common use in the U S."

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The American Society for Pharmacology and Experimental Therapeutics

SYMPOSIUM ON ADVANCES IN PHARMACOLOGY RESULTING FROM WAR RESEARCH

A N RICHARDS, CHAIRMAN

THERAPEUTIC APPLICATIONS OF CHEMICAL WARFARE AGENTS

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With the advent of World War II, national scientific resources were organized for offensive and defensive warfare. With the pattern of World War I as the only precedent for the evaluation of the weapons of war, chemical warfare loomed as a potential source of offensive power as well as a measure requiring strong defensive action. Even as the conflict drew to a close the necessity for continued vigilance and sustained effort remained.

The responsibility for preparedness in the medical aspects of chemical warfare was divided between three main groups working in close cooperation: the Committee on the Treatment of Gas Casualties, N R C, under the chairmanship of Dr Milton C Winternitz, working in cooperation with the Committee on Medical Research under Dr A N Richards; Division 9 (Chemistry Division) of the N D R C, under Dr Walter Kirner, which included a subdivision on Physiological Mechanisms under Dr Homer W Smith and the Medical Division of the C W S, under the leadership of Colonel C P Rhoads and Colonel John R Wood. The C M R and N D R C groups

were comprised largely of academic personnel employing established university facilities. On the other hand, the research facilities of the Medical Division of the C W S were greatly expanded for the task at hand. In close collaboration with the American investigators, and indeed preceding them in the initiation of organized effort due to the earlier impact of the war, were various academic groups and military research installations of the British Commonwealth.

Of the innumerable problems associated with chemical warfare two are of outstanding pharmacological interest, namely, the screening of thousands of toxic compounds for their potential value as chemical warfare agents and the elucidation of the basic pharmacological actions of established and promising chemical warfare agents in order to define therapeutic procedures for the treatment of anticipated casualties.

From the start of this vast program emphasis was placed upon basic research under the assumption that only by an understanding of the fundamental mechanism of action of toxic agents could an intelligent approach to problems of therapy be undertaken. Moreover, in the synthesis of new

¹ Major, Sn C, AUS

chemical warfare gases the relationship between chemical constitution and pharmacodynamic action was the focal point of a planned approach. Cooperating in this extensive program were chemists, bio-physicists, biologists, physiologists, pharmacologists and clinicians. As chemical warfare research unfolded, fruitful hypotheses were revealed which literally demanded exploration. The services of the geneticist, chemical embryologist and cytologist were enlisted to help define the kaleidoscopic picture that was developing.

To the pharmacologist this research had special significance for the focal point of the investigations were highly toxic chemical agents or, in other words, highly active drugs. Under the impetus of the war effort drugs were being scruti-

nized in the belief that the toxic action of arsenic on cells was due to the inactivation of essential thiol compounds. If a thiol could be synthesized which formed a less dissociable complex with arsenic than that formed with natural cellular constituents, it should possess significant antidotal value. The efficacy of monothiols in this regard is well as their limitations were earlier demonstrated by Voegtlin (1) and by Eagle (3).

The notable advance contributed by the pioneer British investigations was the demonstration by Stocken and Thompson (4) that the dithiols were much more effective in reversing the inhibitory effects of arsenic on SH containing enzyme systems than monothiols. Outstanding in this regard was 2,3-dimercaptopropanol, now more familiarly

TABLE 1

The protection of rabbits against an acute lethal dose of mapharsen (20 mg/Kg) by a single intravenous injection of BAL and the absence of such protection with cysteine or glutathione (after Eagle 1942-1943)

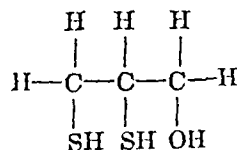
—SH COMPOUND USED TO DETOXYF MAPHARSEN	MG/KG	OUTCOME		PROTECTIVE DOSE OF —SH COMPOUND		
		Dead	Survived	>PD ₅₀	PD ₅₀	
Cysteine	800	2	0	>500 mg/Kg	>500 mg/Kg	No protection even with doses approaching the lethal level, and representing a 15 to 60 fold molar excess relative to the arsenical
	400	6	0			
	200	4	0			
Glutathione	400	2	0	>400 mg/Kg	>400 mg/Kg	
	300	1	0			
	200	1	0			
BAL	36	0	4	25 mg/Kg (0.20 mM / Kg)	7.5 mg/Kg (0.06 mM / Kg)	A lethal dose of mapharsen was neutralized <i>in vivo</i> by one to three molar equivalents of BAL
	24	0	3			
	12	1	2			
	6	2	1			
	2.4	2	1			
0 (Controls no —SH com- pound)	0	5	0			

nized by groups of divergent interests with the elucidation of fundamental mechanisms of action as one of the goals. As might be expected from such a program, therapeutic applications for many of the agents suggested themselves. The following is a brief review of the status of three compounds which have received clinical evaluation. Unfortunately in such a brief review the basic contributions of many investigators must remain unmentioned.

BAL (BRITISH ANTI-LEWISITE)

Early in the course of the war, British investigators turned their attention toward the synthesis of antidotes effective in neutralizing the actions of the arsenical vesicants. On the basis of the classical studies of Voegtlin and associates (1), Peters and coworkers (2), as well as subsequent contributions, antidotes were sought among the mercap-

known as BAL (British Anti-Lewisite) which has the following structural formula:



In a short time American investigators joined the British in research on BAL (5). The technical difficulties of large scale synthesis were solved to yield a chemically pure product of minimal toxicity. Numerous groups devoted their efforts to a study of the pharmacology and toxicology of BAL (6, 7). Various congeners of BAL were synthesized. Of these, BAL glucoside, first prepared by Danielli and coworkers (8) may prove to be less toxic and at least as active therapeutically. Largely through the efforts of Eagle and his asso-

erates (9) stable preparations of BAL in oil suitable for intramuscular administration were developed, for it was early recognized that BAL was highly effective against experimental systemic arsenic poisoning as well as the local effects of arsenical vesicants.

As an example of the efficacy of BAL in the treatment of systemic arsenic poisoning the data of Eagle and associates (9) are presented in tables 1 and 2. Clearly evident is the outstanding activity of a dithiol in comparison with a monothiol and the fact that BAL therapy is effective even if delayed for several hours following the administration of an arsenical.

The fact that BAL was effective in experimental arsenical poisoning prompted its clinical trial

TABLE 2

The efficacy of intramuscular BAL in the treatment of systemic phenyl arsenoxide (hydrolyzed phenyldichloroarsine) poisoning in rabbits (after Eagle, Magnuson and Fleischman, 1944)

Treatment with BAL (in peanut oil) was begun 2 hours after the injection of the arsenical and given in 4 equal doses at 4 hour intervals, followed by single daily injections at the same dosage level, for 3 days

PHENYL ARSENOXIDE mg/kg (1 1/2 times the LD ₅₀ dose)	BAL DOSAGE		NO OF RAB BITS	DIED	SURVIVED	PER CENT OF ANIMALS SURVIVING*
	Mg /Kg, injection	Total in first 24 hours				
2.2	5	20	6	3	3	50
	2.5	10	6	2	4	67
	1.25	5	6	4	2	33
	Controls (No BAL)		7	7	0	0

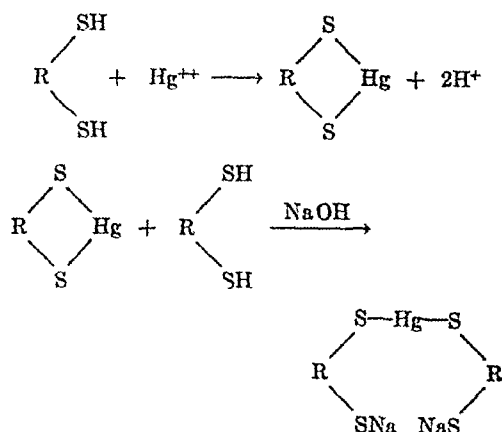
*Alive and well after 30 days. Untreated controls died in 14 hours to 6 days

That humans could tolerate effective doses of BAL was soon established (9, 10, 11). Although the intramuscular administration of 5.0 mg/Kg of BAL in oil may cause the patient some discomfort in the form of lacrimation, burning of the lips, dryness of the mouth and throat, generalized muscular aching, restlessness and nervousness, no severe reactions have been encountered and the effects of smaller doses are minimal. The untoward reactions to BAL seldom persist for more than 30 minutes and injections can be made at intervals of four hours.

BAL has been employed clinically in the treatment of the various arsenical reactions accompanying syphilotherapy, including arsenical encephalitis, dermatitis, agranulocytosis, fever and jaundice (9). Although the final evaluation of BAL must await more extensive study, early reports indicate a dramatic amelioration of symptoms and

a marked reduction in expected mortality. Accompanying the use of BAL in both experimental and clinical arsenical poisoning there is a precipitous increase in the excretion of arsenic which follows immediately after the injection of the thiol (9).

That BAL might prove effective in the treatment of poisoning by other heavy metals was early appreciated. Extensive studies on the antidotal effects of BAL in experimental mercury poisoning (12) have revealed a striking antagonism. The reaction of one mol of BAL with one of Hg^{++} *in vitro* results in the formation of an insoluble mercaptide which can be solubilized by the addition of another mol of BAL to yield a complex of extremely low dissociability. The reaction may be depicted as follows:



It is believed that the efficacy of BAL in the treatment of mercury poisoning is due to the rapid formation and excretion of this relatively undissociated soluble complex.

The results obtained with BAL in the treatment of experimental mercury poisoning in rabbits and dogs are presented in tables 3, 4 and 5. Again the efficacy of therapy is decreased the longer treatment is delayed. However, protection could be afforded dogs as late as two or three hours after the intravenous, and five hours after the oral administration of mercuric chloride. In those experiments in which mercuric chloride was given orally the dogs invariably had a severe diarrhea before the initiation of treatment. No supportive therapy was afforded, nor was lavage performed. The secondary effects of dehydration and electrolyte loss had to be corrected by voluntary consumption of food and fluid. In spite of this severe test the majority of animals recovered even when treatment was delayed for 5 hours and in most instances death was unassociated with renal insufficiency but rather was the result of the severe gastroenteritis which often was advanced before the first dose of BAL was administered.

The successful treatment of experimental mercury poisoning by BAL was the prelude to its clinical trial in human poisoning by Longcope and Leutscher (13). The first case was not seen until 13 hours after the ingestion of mercury, was treated with inadequate doses and succumbed.

TABLE 3

The effect of mercaptan therapy in rabbits following the intravenous administration of an LD₅₀ of HgCl₂

INTERVAL BEFORE INITIATION OF THERAPY	DOSE OF THIOL		MORTALITY
	BAL	BAL glucoside	
min 5	mM /kg	mM /kg	
	3 × 0.1		0/10
	3 × 0.05		0/0
		3 × 0.1 3 × 0.05	0/10 1/10
30	3 × 0.1		2/10
	3 × 0.05		5/10
		3 × 0.1 3 × 0.05	4/10 4/0
60	3 × 0.1		10/10
	3 × 0.05		5/10
		3 × 0.1	5/10

TABLE 4

The effect of BAL and BAL glucoside therapy (3 × 0.05 mM /kg) in dogs receiving 4.0 mg /kg of HgCl₂ intravenously (>LD₅₀)

TIME OF INITIATION OF THERAPY IN HOURS		NO. OF ANIMALS	ACUTE PULMONARY DYSMORPHIA	SUBSEQUENT MORTALITY
BAL	BAL glucoside			
		23	1	22/22
1 1 2		13 13 5	6 6 1	0/7 4/7 1/4
	1	4	0	0/4
	2	6	0	1/6
	3	8	0	0/8

Thereafter, with improved therapy, to the time of this writing, 26 successive cases have recovered uneventfully. Of these 11 ingested 15 grams of mercuric chloride or more. The most striking features of BAL therapy have been the prompt relief of even the most alarming symptoms, the rapidity with which the patients made a complete recovery and the low incidence of significant renal complications.

FLUOROPHOSPHATES

From the pharmacological point of view some of the most interesting compounds investigated during the course of chemical warfare research

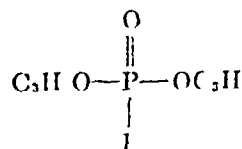
were derivatives of fluorophosphoric acid. The fluorophosphates as a group inhibit cholinesterase. Sodium fluorophosphate itself possesses this action to a significant degree. However, if alkyl groups are substituted for the hydrogen, anticholinesterase activity is greatly enhanced and the compounds become highly lipid soluble. One of the

TABLE 5

The effect of BAL and BAL glucoside therapy (3 × 0.05 mM /kg) in dogs receiving 4.0 mg /kg of HgCl₂ orally (>LD₅₀)

TIME OF INITIATION OF THERAPY IN HOURS		MORTALITY	INCIDENCE OF REFUSAL TO SURVIVE IN A 15 HOUR PERIOD
BAL	BAL glucoside		
		10/10	15/15
2		4/10	1/10
3		7/15	2/9
5		2/5	2/5
	2	1/8	0/8
	3	2/4	0/4

most active members of the series is di-isopropyl fluorophosphate which has the following structural formula:



Di-isopropyl fluorophosphate (DFP) is not only highly active as an anticholinesterase, but of greater interest and significance is the fact that the inhibition of cholinesterase is irreversible (14). Thus, only by the synthesis of new enzyme can the ability to hydrolyze acetylcholine be restored (15, 16). The compound, therefore, possesses great potentialities both as a research tool and therapeutic agent. For example, by the use of DFP not only can pharmacodynamic action be directly correlated with the level of tissue cholinesterase, but also the rate of regeneration of the enzyme in various tissues can be studied. What is more, the chronic effects of reduced cholinesterase activity can be readily followed (16). It is not possible at this point to give a detailed account of the significant facts which have already been revealed by experimental studies on DFP, but a few of the more pertinent observations will be presented.

Sensitivity of cholinesterase to inhibition by DFP
In figure 1 are shown the concentrations of DFP necessary to inhibit the cholinesterases from various tissues in the rat. Of particular interest is the high susceptibility of the serum cholinesterase. This has been evident in almost every species studied.

In view of the high susceptibility of serum cholinesterase it is not surprising to observe that following the injection of DFP it is possible completely to inhibit the enzyme in the serum without significantly affecting that present in other tissues. As might be expected, no pharmacological response accompanies the inactivation of serum cholinesterase alone. This fact demonstrates the fallacy of relating the pharmacological action of anticholinesterase drugs to the effects on an enzyme not directly concerned with the destruc-

tion of acetylcholine at the site of its release. Moreover, it has been revealed that close to 80 percent of the cholinesterase present in the nervous tissue and muscle of experimental animals must be inhibited before marked derangements in synaptic transmission are evident (16). Tissues regenerate cholinesterase at a characteristic rate. In all species studied serum cholinesterase is completely regenerated within a period of a few weeks. Several months are required, however, before the enzyme in brain and muscle returns to its pre-injection level. It is of interest that the cholinesterase in red cells reappears only as a result of erythropoietic activity. Thus, the time for the replacement of red cell cholinesterase is a measure of the life cycle duration of the erythrocyte and varies from approximately 10 days in rats to 100 days in humans (15, 16).

The effect of DFP on transmission of the nerve impulse. DFP should prove to be a highly useful drug for the elucidation of many problems concerned with the role of acetylcholine in the transmission of the nerve impulse. Studies on synaptic transmission have not yet been undertaken. However, DFP has been applied as a research tool to determine the effects of the inhibition of cholinesterase on conduction in nerve fibers as revealed by nerve action potentials. It has been shown that in the isolated sciatic nerve of the bull frog no disturbance in conduction results from the complete destruction of cholinesterase (17), a finding which is scarcely compatible with theories which assign to acetylcholine a significant role in axonal conduction.

Therapeutic applications. DFP immediately suggests itself as a possible therapeutic agent in the treatment of myasthenia gravis, glaucoma, and other conditions subject to symptomatic relief by the inhibition of cholinesterase. Studies in myasthenic patients have been conducted by Comroe and associates (18) and Harvey and coworkers (19). These investigators have shown that DFP is not only capable of increasing muscle strength in this myopathy, but also the effects are much more prolonged than those obtained with prostigmine. However, undesirable side actions, especially on the gastro-intestinal tract, preclude the possibility of giving maximally effective doses. However, Harvey and coworkers have injected DFP directly into the radial artery of myasthenic patients and in this manner obtained a maximal local effect without systemic action. Muscle strength was greatly increased for a period of days. This observation permits the prediction that could an irreversible anticholinesterase be obtained with a predominant action on the myoneural junction, a significant advance in the treatment of myasthenia would result. It is hoped that such a compound will be found in one of the congeners of DFP.

DFP has been employed in the treatment of glaucoma by Leopold and Comroe (20). Not only is it superior to other miotics in reducing intra-ocular tension, but in addition it possesses the outstanding advantages of being non-irritating and having a long duration of action. Thus, for continued effect, instillation of the drug can be made at intervals of days rather than hours.

NITROGEN MUSTARDS

The nitrogen mustards (*bis* and *tris* betachloroethyl amines) are the nitrogen analogues of sulfur mustard (*bis* betachloroethyl sulfide). Their structure may be depicted as follows in which R represents a variety of alkyl groups.

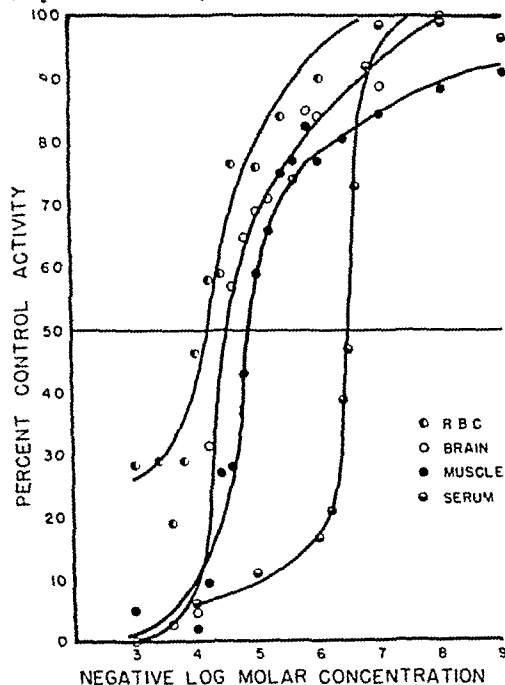
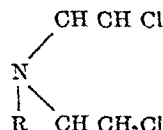


Fig. 1 The inhibition of rat cholinesterase by diisopropyl fluorophosphate in vitro.

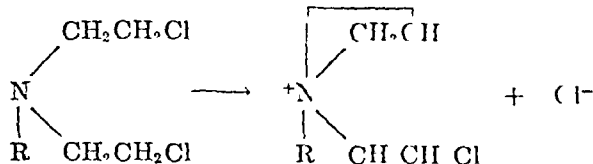
tion of acetylcholine at the site of its release. Moreover, it has been revealed that close to 80 percent of the cholinesterase present in the nervous tissue and muscle of experimental animals must be inhibited before marked derangements in synaptic transmission are evident (16).

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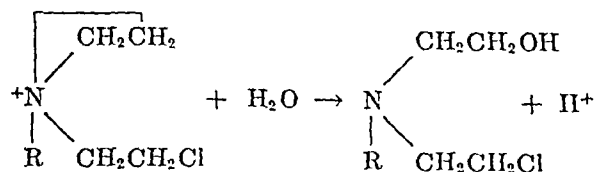
The effect of DFP on transmission of the nerve impulse. DFP should prove to be a highly useful

The nitrogen mustards were synthesized in the search for more effective vesicant war gases. Intensive investigations on their pharmacological actions have revealed facts of fundamental importance which apply not only to the nitrogen mustards, but to sulfur mustard as well, in that both types of compounds possess similar chemical and pharmacological properties. Pertinent to the present discussion was the finding that the nitrogen mustards, in addition to being local vesicants, readily penetrate the skin to reach the circulation and exert generalized systemic actions. These actions can be compared with those of no other drug but in many ways resemble those of X-ray. Extensive investigations on the nitrogen mustards were conducted by numerous workers both in this country and abroad. Only a few of the contributions can be mentioned at this time. A more complete review is to be published (21), wherein the researches of individual investigators may be found.

Chemistry The nitrogen mustards owe their physiological activity to a single chemical reaction which they all share. The active members of this series can undergo intra-molecular cyclization in a polar solvent to form a cyclic ethyleniminium cation. The reaction may be depicted as follows:



The ethyleniminium cation reacts readily with anions and various uncharged nucleophilic molecules. It is this property which presumably imparts to this group of compounds their varied action. In pure aqueous solution at physiological hydron concentration, the ethyleniminium cation reacts with water in the following manner:



If other substances are present, however, they can react competitively. So reactive are some compounds that in their presence, reaction with water is negligible. Among the compounds of biological importance which readily react may be mentioned the alpha-amino, imidazole, sulfhydryl, sulfide, phenolic, epsilon-amino and imino groups of amino acids and peptides, inorganic phosphate as well as glycerophosphate and hexose phosphates, the amino groups of adenosine and thiamine, and the pyridino-N of nicotinic acid amide and pyridoxine. Alkylation of proteins including insulin,

hemoglobin, gelatin, crystalline egg albumin, tobacco mosaic virus, ovalbumin and protamine, as well as various crystalline enzymes has also been demonstrated to occur. The implication that the systemic toxic action of the nitrogen mustards is due to the reaction with any single compound mentioned above is not intended. However, the likelihood that the basic mechanism of the cytotoxic action of the nitrogen mustards involves a similar reaction with a vital cellular constituent is great.

Cytotoxic action The outstanding systemic action of the nitrogen mustards is that which causes, in a manner still unexplained, the death of cells. As a generalization it may be stated that cellular susceptibility is related to proliferative activity. Thus, the formed elements of the blood first reflect the cytotoxic action of the nitrogen mustards (22). This is reflected in a lymphopenia, granulocytopenia, thrombocytopenia and moderate anemia. The mucosa of the gastrointestinal tract is also vulnerable and lethal doses of the nitrogen mustards cause a profuse bloody diarrhea (23). The outstanding pathological lesions are observed in the lymphatic tissue, bone marrow and intestinal tract (24). Lymphatic fragmentation may be evident within 10 hours leading to a persistent lymphatic atrophy for a number of days. The bone marrow becomes progressively depleted and eventually almost complete aplasia results. The intestinal lesion progresses from vacuolization and nuclear swelling of the epithelial cells to eventual necrosis and desquamation with hemorrhage. With sufficiently high concentrations of the nitrogen mustards, cytotoxic action may be exhibited in any cell, without relation to mitotic activity. This accounts for the action of these compounds as contact vesicants.

Nucleotoxic action of the nitrogen mustards The pronounced cytotoxic action of the nitrogen mustards has focussed attention on the morphological changes exhibited by susceptible cells. As a result it has been shown that the mitotic activity of a variety of cells from representative unicellular, invertebrate, amphibian, and mammalian organisms is peculiarly sensitive to inhibition by the nitrogen mustards. As an example may be cited the profound disturbances produced by the nitrogen mustards on the structure and function of chromosomes in *Drosophila melanogaster* (25). Exposure of both male and female adults to sublethal doses was found to reduce or suppress fertility through disturbances of meiosis and mitosis in the gametogenesis of both sexes. However, following exposure of adult males to low doses which did not reduce fertility unduly the genetic analysis of the X-chromosomes revealed a high incidence of sex-linked lethals greatly in excess of the natural rate of mutation, as well as a signifi-

ent number of translocations and inversions. No other class of chemical agents has been shown to have such specificity of action on chromosomal mechanisms. Indeed, in the past, similar effects have only been obtained by the use of X-ray and ultraviolet.

As an example of the nucleotoxic action of the nitrogen mustards in mammalian tissue the effects of low concentrations on the corneal epithelium may be cited (26). Mitotic arrest occurs during the resting phase of the mitotic cycle with the result that the corneal epithelium can be largely depleted of mitotic figures for several days. This occurs without visible evidence of concomitant cytoplasmic or nuclear damage.

Inactivation of enzymes by nitrogen mustards
The fact that diverse cells and tissues which have been subjected to the toxic effects of the nitrogen mustards evidence marked metabolic defects has fostered the theory that the primary mechanism of action is the inactivation of essential cellular enzymes (27). To test this theory a wide variety of enzymatic systems has been studied. The majority proved to be only moderately sensitive to the nitrogen mustards. Those which proved to be highly sensitive were hexokinase as well as creatine and pyruvate phosphokinase, inorganic pyrophosphatase, adenylic acid deaminase and choline oxidase. However, the fact that there has been little correlation between the susceptibility of enzyme systems *in vitro* and *in vivo* has delayed the acceptance of the enzyme inactivation theory of nitrogen mustard intoxication.

Clinical applications
The marked effects of the mustards on lymphoid tissue coupled with the finding that actively proliferating cells are selectively vulnerable to the cytotoxic action of the mustards suggested the therapeutic use of these compounds in the treatment of neoplasms of lymphoid tissue. Nitrogen mustards in the form of their hydrochloride salts are water soluble, crystalline compounds, which can be readily dissolved in sterile saline for intravenous administration. Experiments on transplanted lymphosarcoma in mice revealed that dissolution of such tumors could be rapidly effected although the dose required bordered on the toxic, and the tumor invariably returned (28). The first clinical trial of the nitrogen mustards was conducted on a group of 6 patients in the terminal stages of various neoplastic diseases (29). In two cases of lymphosarcoma in which X-ray therapy had been discontinued, a rapid dissolution of large tumor masses followed a course of injections. The results were sufficiently encouraging to warrant further clinical experimentation. To date approximately 150 patients have been treated by several groups of investigators (30, 31, 32). For the most part observations have been limited to selected cases of Hodgkin's Disease, lymphosarcoma and leukemia.

The clinical results obtained by the individual groups will be published as a symposium in the near future. In the meantime the findings may be summarized in general terms. The most favorable effects have been obtained in patients with Hodgkin's Disease. Remissions characteristic of those which follow careful X-ray therapy have been observed. Symptoms were quickly alleviated and physical evidence of lymphadenopathy, splenomegaly and hepatomegaly regressed. It was necessary to repeat the treatment at intervals varying from 1 to 8 months. Less favorable results have been obtained in cases of lymphosarcoma. The response in acute and lymphogenous and myelogenous leukemias has been disappointing.

The action of the available nitrogen mustards on lymphoid tissue has not yet reached that degree of specificity which precludes undesirable actions on the hemopoietic system. At present dosage is limited by the occurrence of moderate granulocytopenia, thrombocytopenia and anemia. However, with careful regulation of dosage an adequate clinical response is usually obtained without affecting the formed elements of the blood to a serious degree. In addition nausea and vomiting are very likely to occur for a brief period after each injection. No other undesirable effects on the gastro-intestinal tract have been observed.

Although some patients receiving nitrogen mustards have been observed for a period of 28 months, the evaluation of the clinical status of this group of compounds will require many more years of careful study. At present there is no basis for assuming that the therapeutic efficacy of the nitrogen mustards is any greater than that of X-ray.

It is possible that the potential value of the nitrogen mustards in the treatment of neoplastic diseases will only be fully realized when the opportunity to explore the relationship between chemical constitution and pharmacodynamic action has been exhausted. At present only two of the nitrogen mustards have been investigated clinically, namely, *tris* (beta-chloroethyl) amine and methyl bis (beta-chloroethyl) amine. These have been the product of a screening program designed for the evaluation of toxic chemical warfare agents rather than of compounds of therapeutic interest. Literally hundreds of congeners remain to be synthesized and evaluated. Thus a series of compounds which can reproduce in many ways the cellular effects of X-rays is available for chemical and biological investigation. It may be hoped that the previous successes which have characterized the evolution of chemotherapeutic agents by chemical alteration of a parent compound may be duplicated in the case of the beta-chloroethyl amines. The result would be a compound having a sufficiently specific toxic action for certain types of proliferative cells to possess therapeutic value.

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INSECTICIDES AND RODENTICIDES

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In the latter part of 1941, when the active participation of the United States in World War II appeared inevitable, the Division of Preventative Medicine of the Surgeon General's Office of the Army urged the Committee on Medical Research of the OSRD to sponsor the development of superior insecticide preparations for the armed forces. The urgency of this program was manifest by the anxious concern over the anticipated exposure of American troops to insect-borne diseases like typhus, malaria, dengue, and filariasis. Thus shortly after Pearl Harbor the Bureau of Entomology of the Department of Agriculture with the support of the CMR organized a laboratory at Orlando, Florida to search for potent lousicides, larvicides, insect repellents, and lethal agents for the eradication of adult mosquitoes. During its profitable existence this laboratory and other units within the Bureau of Entomology have screened over 7,000 com-

pounds for lethality and repellency against a wide variety of insect pests and vectors of human disease. Compounds were cooperatively supplied by various industrial, university, and government laboratories.

Before potentially useful insecticides and repellents could be released for use by the armed services, careful studies of the toxicology of these agents in mammals became necessary. Accordingly, early in 1943, the CMR obtained the services of the Division of Pharmacology of the Food and Drug Administration under the able and tireless leadership of Dr. H. O. Calvery. Later the important work of the Food and Drug group was augmented by others principally from within the National Institute of Health of the U. S. Public Health Service.

The growing success and the magnitude of the problems arising from this cooperative venture led, in the fall of 1944, to a reorganization within the OSRD of all research projects involved in insect control. The Insect Control Committee

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was formed within the O S R D to act as a coordinating body and to advise interested medical authorities within the armed forces. More recently the Insect Control Committee by transfer to the auspices of the National Research Council has acquired permanent peace time status. It was also during the latter part of 1944 that the Chemical Warfare Service of the Army and many of its associated university laboratories within the N D R C and C M R offered the unique services of an organization designed for the chemical offense of the human species to the more pressing chemical campaign against the insect pest.

Paralleling the search for new insecticides investigators within the Fish and Wildlife Service and certain groups within the C M R were actively engaged in developing more potent rodenticides for the armed services. At the outbreak of World War II the known rodenticides had either been limited in availability or were none too effective. In the summer of 1944, the Division of Chemistry of the N D R C made available for these investigations many compounds which had for various reasons been discarded as candidate agents in an extensive screening program designed originally to develop new war gases. Later all the rodenticide research was brought under the auspices of the Insect Control Committee.*

It is not possible in this brief review to mention the many facets of the overall research program described above nor give deserving credit to the various groups of civilian and military investigators both in this country and in the British Commonwealth, who were enlisted against the insect and the rodent before the termination of World War II. Rather, the present review is devoted to notable topics of lasting pharmacological interest derived from recent insecticide and rodenticide investigations. To the credit of the leaders of this war research basic studies on the mechanism of action of the toxic insecticides and rodenticides were encouraged in the midst of the more urgent practical search for new chemical controls of the pests of humans. Full support was given the concept that such basic biochemical and physiological knowledge could promote the development of agents having specific toxicity for insect and rodent pests and contribute profitably to the investigation of therapeutic controls for possible human intoxication resulting from the wide spread use of these agents.

* It is appropriate to express appreciation to Drs. C. C. Stock and R. A. Ormsbee of the Insect Control Committee, National Research Council, for their clarification of the organizational background of wartime research in insecticides and rodenticides.

INSECTICIDES

DDT The outstanding contribution of the cooperative effort mentioned above was the development of the now familiar insecticide, DDT, 1-trichloro-2,2 bis(para chlorophenyl) ethane (See various publications of the Bureau of Entomology, U S D A, in the Journal of Economic Entomology for 1944 and 1945.) In addition to its anticipated value as an important agricultural and household insecticide, DDT has already proved to be a potent medical weapon for the control of insect borne disease. Convincing and often dramatic results have attended the use of lousicidal powders containing DDT in the prevention of wide spread epidemics of typhus fever among civilian populations of devastated areas of Europe (1). Moreover, while already foreshadowed by observations made during the course of the war, the wide spread use of the agent in mosquito-infested areas may be expected to effect significant reductions in the incidence of mosquito-borne diseases.

Among the more important characteristics of DDT is its relatively low toxicity for mammalian species. It is highly insoluble in water and is not readily absorbed from the gastro intestinal tract or skin. In most laboratory mammals the minimal lethal dose, following oral administration of DDT dissolved in edible oils, is several hundred milligrams per kilogram (2, 3, 4, 5). Even after intravenous administration of emulsions of DDT, acutely lethal doses are of the order of 50 mg./Kg. (6). On the other hand, the agent is readily absorbed from the surface of the insect body and the external application of 10 to 20 mg./kg is fatal to insects like the cockroach (*Periplaneta americana*) and the housefly (*Musca domestica*) (7).

The general pharmacology of DDT in mammals is at present reasonably well known. However, the specific events to be expected in cases of human intoxication can only be predicted from observations of laboratory animals. In spite of the extensive employment of the agent in the past few years, no positive instance of human poisoning has been verified. Several hundred suspected cases of intoxication have been scrutinized carefully, and only in rare instances have untoward findings been reported. These could be attributed to toxic effects of the solvents of DDT and not to the agent itself (8).

The principal pharmacological actions of DDT in both the insect and the mammal are centered in the nervous system. Both groups of animals in response to toxic doses exhibit tremor, postural deficiencies, and extreme convulsions. The typical tremor and convulsions observed in mammals have been generally attributed to the toxic actions of DDT on the central nervous system at levels higher than the spinal cord. More specifically the

tremor, asynergia and dysmetria of poisoned dogs cats, and monkeys resemble clinical manifestations of acute decerebellation (9) and, in fact extensive pathological changes have been observed in the cerebellum of dogs following prolonged chronic administration of DDT (10). Furthermore, electroencephalographic studies of cats and monkeys following acute intoxication have revealed marked electrical changes in the motor cortex and various regions of the cerebellum to a degree suggesting a specific toxic action on cortico cerebellar tracts (11).

While the sensitivity of the higher levels of the central nervous system is the prominent feature of the neurological manifestations of DDT-poisoning in mammals, it is generally conceded that the peripheral nervous system is largely involved in the neurotoxic actions in insects and other arthropods. Local application of DDT in dilute concentration to motor axons can result in spontaneous, multiple electrical discharges with repetitive and tetanic contractions of the innervated muscles (12). Moreover, exposure of proprioceptive, sensory bodies to DDT irritates marked and spontaneous propagated impulses in afferent sensory fibers (13). Although the agent may also act directly on central ganglia (7), the spontaneous electrical activity of the isolated ventral nerve cord of cockroaches remains unaltered after direct application of DDT (13).

In addition to the neurotoxic actions of DDT in mammals two other important pharmacological properties have been observed which appear associated with the fact that the compound is a chlorinated hydrocarbon. Acutely lethal doses sensitize the mammalian myocardium to sympathetic stimulation with the result that ventricular fibrillation is a frequent cause of death in the larger mammalian species (14). Cardiac failure is usually precipitated by DDT-induced convulsive seizures which typically involve a marked sympathetic component. Like other chlorinated hydrocarbons DDT is hepatotoxic and pathological changes are prominent in the livers of chronically poisoned mammals (15, 16, 17).

Considerable attention has been directed toward understanding the basic chemical mechanisms whereby DDT disturbs normal cell function. DDT is for the most part chemically unreactive *in vivo*. Large amounts may be stored for considerable periods in fat depots and only small fractions of doses previously administered are excreted in a chemically changed state (3, 18, 19, 20). Of the postulated intermediates in the metabolism of DDT none is known to be more toxic than DDT itself. The agent has not been found to inhibit enzymatic reactions *in vitro* (21), nor are specific enzymes like acetylcholine esterase inhibited *in vivo* by the administration of amounts

sufficient to cause neurological abnormalities (22, 7). While significant change in the metabolism of carbohydrate are observed in intoxicated mammals (23, 24), these appear secondary to the severe muscular activity manifested by the poisoned animals. Similarly, minor changes have been noted in the metabolism of tissue slices isolated from intoxicated mammals which may be the consequence of a more primary pathological effect of DDT (23, 24, 25).

The relative inertness of DDT toward chemical reaction with living tissues is to be contrasted to the rapidity with which the agent can induce functional changes in susceptible cells. The response of the insect or crustacean nerve to topical application of DDT is immediate (12, 13). Similarly, changes in the electrocardiogram and outward manifestations of poisoning in mammals follow closely upon the intravenous administration of the agent (6, 11). It has, indeed, been suggested that the DDT molecule may act upon nervous structures by rapid physicochemical adsorption at the surface of nerves resulting in disorganization of the surface membrane and derangement of normal nerve function (12).

Hexachlorocyclohexane. Of the many compounds which were surveyed as potential insecticides during the course of the war only 1,2,3,4,5,6-hexachloro cyclohexane has proved to equal and in some instances surpass the toxicity of DDT for various species of insects. This compound, developed largely through the efforts of British investigators, is commonly referred to as 666, to symbolize the empirical formula, $C_6H_6Cl_6$. Technical preparations of 666 are composed of varying proportions of 4 space isomers which differ structurally in the spatial arrangement of the chlorine and hydrogen atoms about the six-membered ring of carbon atoms. The 4 isomers also differ widely in their insecticidal actions. Thus, the gamma isomer known as gammexane, is many hundred times more toxic to insects than any of the other isomers (26, 27).

Likewise the marked difference in activity of the isomers has been noted in mammalian species. Following oral administration gammexane is at least 5 times more toxic than the other isomers (27, 4). Similarly rabbits survive the intravenous administration of 100 mg./Kg. of the delta isomer but succumb to 5 mg./Kg. of gammexane (28, 29). While gammexane is a potent convulsant, the beta and delta isomers appear to be depressant, eliciting marked flaccid paralysis in rabbits without concomitant signs of central stimulation (20). Moreover, the prior administration of the delta isomer can largely antagonize the convulsant actions of intravenous lethal doses of gammexane and thereby effect a severalfold reduction in its toxicity (29).

REPELLENTS AND MITICIDES

Among the diverse measures adopted to protect troops against infection with mosquito borne parasites was the employment of potent repellent chemicals to prevent adult insects from coming in contact with human hosts. The repellents receiving wide application were dimethyl phthalate, n-butyl mesityl oxide oxalate and 2-ethyl-1,3-hexanediol. In using these agents small amounts are spread over the exposed skin, and tightly fitting regions of clothing or are impregnated into outer garments. After application they afford relief from insect bites for variable periods of time. The exact mechanism whereby these agents actively repel the adult insect with only minimal stimulation of the human sensorium remains an interesting topic for future investigation.

In addition to the repellents of flying insects several compounds were investigated as effective miticides, namely dimethyl and dibutyl phthalates and benzyl benzoate. When these are spread over or impregnated in outer garments they protect against the bites of chiggers and tropical mites which transmit scrub typhus. Earlier English observations of the effective scabidicidal action of benzyl benzoate were also confirmed.

RODENTICIDES

Investigations dealing with the development of improved rodenticides were largely concerned with three agents: red squill, alphanaphthyl thiourea (ANTU), and sodium fluoroacetate (1080). The two latter compounds were products of wartime research, whereas red squill had enjoyed extensive use as a standard rodenticide before the war. Since red squill is relatively non-toxic to humans and domestic pets, it is highly regarded as an effective rodenticide for use by untrained personnel. However, red squill is not a native plant and import restrictions due to wartime exigencies largely curtailed its employment during the war. In an attempt to secure an unlimited supply of the plant material to meet all future emergencies a program was instituted to assay and select bulbs of highest potency for propagation in this country (30). It was also hoped that toxicity might eventually be enhanced by selective cross breeding of the more potent stocks. Some attention was given to the isolation of the active principle of red squill for purposes of pharmacological study and the development of methods of chemical assay and synthesis (31). Accordingly scilliroside was isolated and shown to be a highly toxic glycoside which shares the pharmacological properties of typical digitalis glycosides in the cat (32).

Alphanaphthyl thiourea (ANTU) (33) and sodium fluoroacetate, which is to be discussed directly, are considerably more toxic to rats than is red squill.

The lethal oral dose of ANTU for the Norway rat is about 5 mg/Kg. The agent is odorless and practically tasteless and, therefore, acceptable to rats when distributed in baits. Animals will even ingest lethal doses while preening themselves after contamination of their feet and fur in runways and nests dusted with ANTU. By means of the agent very effective control of rat populations has been established over wide areas of certain urban communities. ANTU is relatively non-toxic to humans, the lethal oral dose being estimated as greater than 1 gm/Kg on the basis of studies in monkeys (33). Furthermore, no instance of human intoxication has been observed during a period of several years, in which more than 500,000 people have had occasion to be exposed to the rodenticide (33).

ANTU exhibits many interesting pharmacological properties which, as yet, remain largely unexplained. The toxicity of the agent for different mammalian species varies widely and cannot be predicted in terms of taxonomic relationships. For example, among common rats the Norway species (*R. norvegicus*) and most strains of albino, laboratory animals are highly sensitive to the agent whereas the black (*R. rattus*) and Alexandrine (*R. alexandrinus*) species are relatively resistant (33, 34). Indeed other rodents fail to exhibit unusual sensitivity to the agent and the lethal oral dose in the rabbit, albino mouse, field mice, ground squirrels, and prairie dogs is at least 10 to 100 times that observed in the Norway rat (34). Thus the applicatory value of ANTU as a rodenticide is limited almost entirely to the control of the latter species. Among the carnivores, the sensitivity of the dog resembles that of the Norway rat, but the cat is a more resistant species (33, 34). The lack of predictability in the susceptibility of various mammalian species has rendered somewhat uncertain a final decision concerning the toxicity of ANTU for humans on the basis of the relative resistance of monkeys.

Another pharmacological action of ANTU, inviting future investigation, is the tolerance to its toxic action which rapidly develops and persists for several weeks in animals receiving sublethal doses (33, 34). Within 3 hours after the administration of a sublethal dose rats may already exhibit tolerance to lethal amounts of the agent. By means of the chronic administration of progressively increasing doses of ANTU, tolerance has been achieved in rats to amounts which are equivalent to 50 times the acute lethal dose in untreated animals (33). After cessation of chronic dosage resistance to ANTU subsides and disappears within a month.

The susceptibility of Norway and albino rats also depends on the diet and age of the animals. Diets high in protein or containing supplements

of cystine enhance resistance to ANTU (33). Moreover, a 40-fold increase in susceptibility may be observed during the development of young albino rats through the stage of puberty, which in itself is marked by a pronounced loss in resistance (34).

The characteristic acute action of ANTU is an untoward effect in the lungs which permits an excessive leakage of plasma constituents into extravascular spaces. Pulmonary edema and pleural effusion are observed at autopsy, the thoracic cavity containing large amounts of fluid (33). Plasma proteins appear abundantly in the effusion concurrent with their loss from the circulating blood (35, 36). During the course of fatal, acute intoxication lymph flow from the thoracic region increases rapidly and markedly (37). Since there is no concomitant rise in peripheral venous or right intra atrial pressure (38), the enhancement of thoracic lymph flow and the appearance of pleural effusions can be attributed to an increased permeability of pulmonary and possibly pleural capillaries.

While the pulmonary lesions produced by ANTU are the most striking feature of acute intoxication, other effects have been observed. Cats receiving chronic lethal doses eventually develop a fatal jaundice without a marked involvement of pulmonary structures (35). Terminal bilirubinemia is not associated with a significant anemia but rather derives from an intrahepatic obstructive jaundice. Dogs which have been rendered tolerant to ANTU as the result of chronic administration exhibit a six-fold increase in serum cholesterol (36). This finding has been related to observed elevations of serum cholesterol following chemical thyroidectomy with thiourea. Indeed, the chronic effects of ANTU on the thyroid gland are similar to those of thiourea and 2-thiouracil. Lastly the chronic administration of ANTU to rats can result in reductions in the rate of growth of *hans* as well as an extensive depigmentation of hair and skin (33).

Sodium fluoroacetate The establishment of ANTU as a specific in the control of the Norway rat was succeeded by the development of a second rodenticide, commonly referred to as 1080, which, unlike ANTU, has proved highly effective against an unlimited variety of rodent species (39). Ten-eighty is a relatively simple compound, sodium fluoroacetate, with many desirable properties advantageous to its successful application as a rodenticide. Among its more important features are high toxicity for rodents in general, chemical stability, ease of admixture with standard baiting materials, and absence of objectionable odor or taste, permitting satisfactory acceptance by baited animals. As the result of numerous practical trials it has been demonstrated that 1080 is the

most satisfactory agent available for the control not only of domestic pest like rats and mice, but also of all varieties of field rodents.

A serious objection to the adoption of 1080 as an all purpose rodenticide is its high toxicity for all mammalian species, a disadvantage which may deter its handling by any but trained personnel. While different species of mammals are variably sensitive to fluoroacetate, resistance of any given species is only relative. Dogs succumb to doses as low as 0.1 mg./kg. and the minimum lethal dose is less than 1 mg./kg. in many species which include the rabbit, guinea pig, cat, pig, goat (40), and certain wild rodents like the Norway rat (33, 39). The Rhesus monkey (*Macaca mulatta*), albino rat, and Syrian hamster are susceptible to doses of the order of 5 mg./kg. (40). Among the most resistant of the mammals is a species of spider monkey (*Uteles* sp.) in which the minimum lethal dose is about 14 mg./kg. (40). Thus sensitivity among the various mammals may vary a hundredfold.

In addition to observed variations in susceptibility different mammals exhibit widely dissimilar responses to 1080 (40). Thus, the prominent lethal action in species like the rabbit, goat, horse, and spider monkey is a disturbance of myocardial function culminating finally in ventricular fibrillation. Before the onset of ventricular fibrillation various cardiac arrhythmias ensue which by electrocardiographic analysis have been observed to include accentuation and alternation of the T-wave, ventricular tachycardia, and ventricular extrasystoles of both nodal and ectopic origin. Alternation in the electrocardiogram is frequently associated with a 50% pulse deficit. While myocardial dysfunction may represent an exclusive mechanism of lethal action in some species, a few animals like the dog and guinea pig fail to exhibit serious cardiac abnormalities after intoxication and succumb rather to profound stimulation of the central nervous system involving in sequence, hyperexcitability, epileptiform convulsions, exhaustion, and finally respiratory depression. A third group of species, namely, the cat, pig, and Rhesus monkey, respond both to the myocardial and the central nervous actions of the agent. Finally, the albino rat and Syrian hamster represent another variation in response, in that animals, which survive the acute, central nervous effects of fluoroacetate, usually develop a profound and persistent bradycardia before complete recovery is evident.

Attempts to define more precisely the locus of action of fluoroacetate in vulnerable cells has revealed that the agent inhibits specifically the oxidative metabolism of certain intermediates of carbohydrate breakdown (41, 42, 43). Investigations with yeast, bacteria, mammalian tissue

shes and biers, (41), and frog muscle (42, 43) have indicated that the oxidative disposal of pyruvate is impaired probably by inhibition of one of the steps in its dehydrogenation via the citric acid cycle. More specifically, studies with fluoroacetate have revealed that a possible pathway in the oxidative disposal of pyruvate by mammalian tissues may involve a direct oxidation to acetate and CO followed in turn by oxidation of the formed acetate. Thus it has been shown that fluoroacetate inhibits competitively acetate oxidation in various isolated mammalian tissues. Moreover, the oxidation of pyruvate in poisoned tissues results in the accumulation of appreciable amounts of acetate (41).

It is tempting to correlate the biochemical actions of fluoroacetate with the wide variations observed in the susceptibility and physiologic response not only of different species of mammals but also of different tissues within the individuals of any single species. The specificity of biochemical action of fluoroacetate in isolated cells and tissues suggests a similar specificity of biochemical action in intact organisms. Thus, it would appear that cells diverge considerably in their

obligate dependence on the specific metabolic pathways which can be deranged by fluoroacetate.

CONCLUSION

In the course of the above discussion certain of the salient biological actions of recently developed insect and rodent pesticides have been presented. Some of these agents may be expected to receive continued attention from pharmacologists not only because of the future wide spread employment of these toxic chemicals in pest control operations but also because of their interesting pharmacological properties which are relatively unique and, as yet, largely unexplored. Among the latter, to mention but a few, are the specific actions of DDT on the cerebellum and cortico-cerebellar tracts, the pulmonary lesions elicited by ANTU in vulnerable species as well as the remarkable drug tolerance exhibited by animals after chronic administration of this agent, and the myocardial effects of fluoroacetate which in conjunction with its metabolic actions may prove valuable to the better understanding of the intimate relationship between cellular function and cellular metabolism.

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CHEMOTHERAPY OF MALARIA 1941-45

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An extensive program of research in the chemotherapy of malaria has been carried out during the years 1941-1945 by a large group of investigators supported mainly by the Committee on Medical Research of the Office of Scientific Research and Development. This program has involved co-operation with industrial firms and with the Army, Navy, and U. S. Public Health Service. Close coordination was attempted between the synthesis of new compounds, pharmacological and experimental therapeutic investigations of these compounds in animals, and the clinical trial in human malaria of selected compounds under carefully controlled conditions. It is of the pharmacological and experimental therapeutic investigations that I wish to speak; however, I must refer occasionally to the trial of drugs in human malaria in order to give proper interpretation to the animal experiments. I shall be obliged to make use of the unpublished data of many investigators to whom due acknowledgement is hereby made. These data with due credit to the investigators supplying them will be given in detail in a forthcoming monograph entitled "A Survey of Antimalarial Drugs, 1941-1945."

At the outbreak of the war no definite information was available as to the relative value of quinine and quinacrine in the suppression and treatment in malaria. The development of a method for the determination of small amounts of quinacrine in plasma led to better methods for the use of quinacrine. (1) Controlled studies led to the demonstration of the superiority of quinacrine to quinine. (2) Studies attempting to find drugs superior to quinine and quinacrine have involved the screening of over fourteen thousand compounds for various types of antimalarial activity in various avian infections. In addition, studies on the toxicology and pharmacology of many of these compounds were made in laboratory animals, and the potentialities of about one

hundred compounds were explored in human malaria produced by parasites of domestic and South Pacific origin.

The first question to be answered about a compound submitted for test is whether or not it possesses antimalarial activity. The research which led to the discovery of the antimalarial properties of pamaquine (plasmochin) and quinacrine (atabrine) was carried out on relapsed malaria in the canary. In these studies quantitative evaluation of antiparasitic activity was attempted by making use of the chemotherapeutic index, a concept introduced by Ehrlich. This is the ratio of the maximum tolerated dose of the drug to its minimal effective dose. It has been considered a measure of the antimalarial value of a drug. Unfortunately, chemotherapeutic indices determined on birds frequently bear no relation to those in human malaria and may be more misleading than helpful. It appeared to be important in future work to test for antimalarial activity in avian infections and to test for toxicity on mammals. Buttle and coworkers (3), in studying the action of the cinchona alkaloids and their derivatives on malarial infections in the canary, expressed activity in figures representing the dose of quinine necessary to produce the same response as a unit dose of the alkaloid under test (the quinine equivalent). This point of view was a definite departure from the chemotherapeutic index measured in birds and used exclusively by the Germans.

A difficulty in the testing of drugs for antimalarial action on avian infections is that host and species of parasite are both different from those involved in the human diseases. In 1943, Curd (4) reviewed the literature on the activity of drugs in avian, simian, and human malaria. Two conclusions may be drawn from Curd's review. First, studies have been conducted in the past on all malarial infections in such a way that results of activity can be expressed only in qualitative terms.

such is no action, doubtful action, slight action, pronounced or definite action. Second, the gaps in our knowledge at that time were so numerous that trustworthy conclusions were difficult or impossible to make.

Without quantitative evaluations of the antimalarial activity in avian infections there can be no adequate judgment of the significance of tests in different avian infections or the relations of these tests to activity in the human malarium. Also, without quantitative data in avian infections there can be no adequate correlations between antimalarial activities and such structural changes as may be introduced in an attempt to obtain the best of a series of compounds. For these and other reasons, the quinine equivalent has been introduced as an expression of antimalarial activity for therapeutic tests.¹ The quinine equivalent is the ratio by weight of the dose of quinine to the dose of the drug under assay when both drugs produce the same response on parasitemia.

Sulfadiazine and certain other sulfanilamide derivatives have been found to be complete causal prophylactics in *Gallinaceum malaria* in the chick (5, 6, 7). Accordingly the potencies of drugs as prophylactics in *Gallinaceum malaria* in the chick can be expressed in terms of sulfadiazine and the sulfadiazine equivalent has been introduced as an expression of antimalarial activity for prophylactic tests in this infection. The sulfadiazine equivalent of a drug is the ratio by weight of the dose of sulfadiazine to the dose of drug under assay when the prophylactic activity of both drugs is the same under identical conditions.

Unfortunately the sulfadiazine equivalent may not be the same when calculated from the dose of sulfadiazine which gives complete protection and when calculated from the dose which produces a significant delay in appearance of parasites over the time of appearance in control birds. Also, with *Lophurae malaria* in the turkey and *Cathemerium malaria* in the canary sulfadiazine has no or only slight, prophylactic effect. It cannot be used here as a standard.

The fact that avian and human malarial infections differ markedly in their respective host-parasite relationships poses the question as to the value of "screening tests" with avian malarial infections for judging antimalarial activity in human malaria. Do these tests discard drugs which may be of value in human malaria and do they indicate high antimalarial activity of drugs which have little or

no value in human disease? In other words, just what do the avian malarial tests mean for the selection of compounds for trial in man? Only a partial answer to these questions can be given.

The antimalarial activity of a drug in an avian infection may differ markedly from that exhibited in a human infection for a number of reasons. Some of these are 1) differences in susceptibility of different species of parasites, 2) differences in absorption, excretion, and/or distribution which result in different blood concentrations of the drug in birds and in humans, and 3) degradation of the

TABLE I
Parasite and host differences in response to drugs
Therapeutic Test
Quinine Equivalents

SN ¹	DUCK		CHICK		MAN
	L	C	L	G	V
8 323	<0.15	1.0	<0.10	2	0.5
7 618	15	60	30	15	5
5 137	3	6	30	20	4
971	60	150	40	10-50	10
1 452	3	10	80	60	
112	2	0.03	2	0.6	0.05
475	1.0	0.06		2	0.03
10 275	20	80	2	2	1.0
6 565	0.15	5	0.06	1.5	<0.2
4 271	2	1.0	1.0	0.6	<0.2
12 610	<0.10		2	0.8	0.2

L = *Lophurae* C = *P. cathemerium* G = *P. gallinaecum*
V = *P. vivax*

¹ The SN number is one which will be used in the monograph to which reference has been made. 112 is sulfadiazine. 475 is forbesin. 2 2 3 3 tetramethyl 1 1'-diphenyl 4 4-bis 3 pyrazole-5-o-dione. 971 is pamaquine plasmodium 8 (4-diethylamino-1-methylbutylamino) 6-methoxyquinoline. 1 452 is 8 (3-amino-propylamino) 6-methoxyquinoline. 4 271 is dimethylidithiocarbamic acid methylester 6 565 is 3 7-diacetamido 5 phenyl phenazinium ion. 7 618 is 7-chloro-4 (4-diethylamino 1-methylbutylamino)quinoline. 8 137 is 1 (7-chloro-4-quinolylamino)-3-diethylamino 2 propanol. 8 323 is 1 (p-chlorophenyl) 2 (4 (2-diethylaminoethylamino) 6-methyl 2-pyrimidyl)guanidine. 10 275 is 6 8-dichloro 2 phenyl- α 2 piperidyl 4-quinolinemethanol. 12 610 is 1 d \ (2-benzoyloethyl)- α 7-diethoxy- β 8-di-methyl-butylamide.

drug to an active product in the bird and not in man or, vice versa, degradation to an inactive product in man and not in the bird.

Similarly, differences in antimalarial activity of a drug on different avian infections may be due to real differences in species susceptibility or to differences in metabolic processes in the hosts. Differences due to species may be determined by using various species in the same host under identical testing conditions, and, vice versa, differences due to host may be studied by testing the same species in various hosts under identical testing conditions.

In table I are given certain selected tests of drugs on three species of parasites in two avian hosts. An attempt has been made to give also the

¹ When assaying the potency of quinierine or pamaquine analogues, it may be convenient to express the activity of these analogues in terms of their quinierine or pamaquine equivalent. These equivalents are defined in the same manner as the quinine equivalent.

antimalarial activity of the drug in vivax malaria in man.² Several important conclusions may be drawn from the data given in table 1. A drug (See SN 5,323) may be completely inactive in lophurae malaria in both duck and chick but have the same order of activity as quinine in gallinaceum malaria in the chick, in cathemerium malaria in the duck, and in vivax malaria in the human. Here the difference is dependent on species of parasite and not on host. Other examples of differences in the susceptibility of species of parasites are seen with drugs SN 112, SN 175, and SN 6,865.

Differences in activity which are dependent on host rather than on species of parasite are seen with drugs SN 1,152, SN 10,275, and SN 12,610. A host difference may occur within a series of chemical compounds where only a side chain is changed. Thus, SN 7,618 and SN 8,137 differ only in that one has a 4-diethylamino-1-methylbutyl and the other a 3-diethylamino-2-hydroxypropyl side chain. SN 7,618 is definitely the more active drug in the duck, but no difference between the activities of the two drugs can be detected in the chick. In man the drugs are of the same order of activity. A drug may have the order of activity of quinine or greater on two or three species of avian parasites and prove inactive in vivax malaria in man (See SN 6,865 and SN 4,271).

From the above data the conclusion has been drawn that for proper screening in avian infections two or more species of parasites and hosts should be used. In addition, this is apparently necessary when one is working within a definite chemical series to find the best compounds for human trial. It is doubtful if compounds of real value in human malaria will be missed if two avian parasites and two avian hosts are used when screening for trophozoite activity of drugs. Moreover, it is impossible to say that any one avian parasite or any one avian host is preferable if only one screening test is to be used. In different chemical series the correlation of activity between avian and human infections varies.

In our discussion of the screening program in avian malaras we have been considering only antimalarial activity against trophozoites in blood-induced infections. One must consider antimalarial activity against other stages in the life cycle of the malarial parasite—sporozoites, cryptozoites (or early tissue stages), exoerythrocytic forms (or late tissue stages), and gametocytes. Studies on sulfadiazine and on quinacrine may be mentioned to illustrate some of the difficulties encountered in the present program. Sulfadiazine is a causal prophylactic against gallinaceum ma-

laria in the chick but cures neither a sporozoite induced nor a blood induced infection. It is not causal prophylactic against lophurae malaria in the turkey or against vivax malaria in man. In knowlesi malaria in the monkey it cures the infection. In vivax malaria it has a low grade of activity and does not cure. In falciparum malaria sulfadiazine is a true suppressive. Quinacrine is neither a causal prophylactic nor a cure in gallinaceum malaria in the chick but is effective in controlling blood induced infections. In knowlesi malaria it is not a cure but is effective against trophozoites. Quinacrine is effective as a cure in blood induced vivax malaria but not in sporozoite induced infections. However, in falciparum malaria quinacrine cures both blood induced and sporozoite induced infections.

The discovery of a true causal prophylactic for human malaria—a drug which would eradicate

TABLE 2
Trophylactic tests in avian and human malaras

SN ¹	GALLINACEUM IN CHICK	LOPHURAE IN TURKEY	CATHEMERIUM IN CANARY	VIVAX IN MAN
112	+++	0	+	0
5,605	+++	-	±	0
5,949	+++	±	±	0
11,437	+++	+++	+	0
971	0	+	+	+++

+++ = Complete protection ± = Significant delay in appearance of trophozoites over controls 0 = No effect

¹ 112 is sulfadiazine 971 is pamaquine, plasmochin 5,949 is 2-hydroxy-3-(2-methoxyethyl)-1,4-naphthoquinone 5,605 is 5-bromo-2-pyrimidinyl-sulfanilamide 11,437 is N-(5-chloro-2-pyrimidinyl)metanilamide

some stage of the parasite before trophozoites were produced—would constitute a great advance in the chemotherapy of malaria. On the other hand, the discovery of a drug which would resemble quinacrine in its antimalarial properties but which, in addition, would cure vivax malaria would probably be of more value than a causal prophylactic which did not cure (e.g., sulfadiazine in gallinaceum malaria of the chick).

Several drugs belonging to different chemical groups have been found to be causal prophylactics in avian infections. However, from the data available at present there seems to be a total lack of correlation between prophylactic activity in avian infections and in vivax malaria in man. In table 2 are given data to illustrate this point.

An assessment of the potential curative value of a drug in human vivax from experiments conducted on the malaras of animals cannot be made at present. A number of studies have been made on the curative effect of drugs in avian malaras and, to a lesser extent, in simian malaras, but

² The antimalarial activity was determined on blood-induced vivax malaria (McCoy strain). For details see Shannon *et al.* (8).

the data at present available do not allow any conclusions as to the correlation of these studies with curative action in human vivax.

On account of this lack of an experimental infection for the screening of drugs as potential curative agents for vivax malaria, the problem of the cure of this human infection has been much more difficult than that of finding a drug superior to quinaquine. Until one or more drugs are found which are curative in vivax malaria, no correlation can be attempted with the experimental malarias of animals. The plan adopted has been to test for curative property in vivax malaria one or more examples of each chemical group showing even slight antimalarial activity.

The discarding of the chemotherapeutic index in the bird necessitates some screening test for toxicity. The antimalarial value of a drug is dependent not only on its antimalarial activity, but also on its toxicity for the host. Emphasis was placed upon the use of mammals for toxicity studies because it may be presumed that the common laboratory mammals are closer to man than birds with respect to some of the processes of absorption, degradation, excretion, etc. Since most new compounds are available in limited amounts the preliminary toxicity tests in mammals are performed on small animals such as the mouse or the rat. These studies on the mouse and the rat have in general correlated roughly with studies on the dog and the monkey and with such information as has been obtained on man. However, in the case of the 8-aminoquinolines, marked discrepancies between the relative toxicities of members of this group have been found when tested on the mouse, the rat, the dog, and the monkey.

Toxicity tests are carried out in a manner to simulate as closely as possible the schedule of dosage to be used in human therapy—curative, suppressive, or prophylactic. Obviously, a determination of the acute toxicity (effect resulting from a single dose of the drug) is of no value in assessing the toxicity of the drug for use as an antimalarial to be given over several days. Thus, the acute toxicity of quinine for mice is equal to or slightly greater than that of quinaquine. On the other hand, a determination of the short-term chronic toxicity (seven, ten, or fourteen day administration) of quinine and quinaquine on both mice and rats indicates clearly that quinaquine is more toxic than quinine. This checks with experience in the human being, since it is well established that, on the basis of dosage, quinine is less toxic than quinaquine. These preliminary toxicity tests on the mouse or the rat are done in such a way as to attempt to maintain a more or less constant concentration of drug in blood and tissues during the whole period of observation. The schedule of dosage necessary to accomplish this will of

course, depend upon the rapidity of absorption, excretion, and/or degradation of the particular drug in question. With many drugs a single oral dose per day will not maintain a concentration of drug in the blood at a desirable level. Two or three equally spaced doses per twenty-four hours can be given or the drug diet method can be utilized (9, 10).

Before a drug is tried in a preliminary way for its antimalarial action in man, additional pharmacological studies in the larger laboratory animals are necessary. In most instances dogs and/or monkeys have been utilized for these additional studies. The characteristic toxic symptoms of the drug are elicited by administration of single doses by mouth or parenterally. With a knowledge of the type of toxic symptoms exhibited by the drug, experiments are performed to determine the short-term chronic toxicity. Here, as in the case of experiments in mice and rats, an attempt is made to have the dosage schedule resemble that to be used in man. Also, some appropriate drug is used as a standard of reference.

If the preliminary trial of the drug in human malaria suggests that further exploration of its value is justified, additional and more detailed pharmacological and toxicological studies in animals are conducted. These may involve studies of long-term chronic toxicity, as well as more detailed studies of the preliminary type.

Some examples may be given to illustrate what has been accomplished in the cases of three or four of the more promising chemical groups. If one takes the formula for quinaquine and removes either of the outer rings, one obtains two 4-aminoquinolines: one with a methoxy group in the 6-position and one with a chlorine group in the 7-position. The first of these compounds belongs to a series which, in its antimalarial properties, resembles quinine and quinaquine rather than the 8-aminoquinoline, pamaquine (11).

About 200 compounds in the 4-aminoquinoline group, with variations in nucleus as well as in side chain, have been screened for antimalarial activity in at least one avian infection. A smaller number have been examined for toxicity in at least one species of mammal. About ten of these 4-aminoquinolines have been examined, first for toxicity in the dog and monkey and then for antimalarial activity and toxicity in the human. Several of these ten appear to be superior to quinaquine. SN 7,618 has received the most extensive study in both civilian and military establishments. It is superior to quinaquine in a number of ways. Effective suppression can be obtained by administering it no more frequently than once weekly in a well-tolerated dose. It will cause an abrupt termination of the clinical attack of vivax malaria and will cure falciparum malaria when administered

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BACTERIAL CHEMOTHERAPY

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Probably never in the history of medicine has scientific and practical progress in any one field been greater than in chemotherapy during the past 10 years, which are marked by the introduction of the sulfonamides and the antibiotic agents. The extraordinary advances become immediately apparent by a comparison of the number of infectious diseases responding to chemotherapy at the beginning of the years 1935, before the introduction of the sulfonamides, 1941, the last pre-penicillin year, and 1946, with the sulfonamides, penicillin and streptomycin at our disposal (table 1). The progress made since 1941 becomes even more impressive, if we compare the safety margin of the newly introduced antibiotic agents penicillin and streptomycin with that of the drugs commonly used before that time.

The short time at my disposal can probably be best utilized by confining the discussion to the antibiotics, which constitute the principal advance in the field of bacterial chemotherapy since 1940. The discovery of this group of agents dates back to Pasteur and Joubert (1), who in 1877 first observed the phenomenon of bacterial antagonism, to Emmerich and Loew (2), who in 1899 first clinically used pyocyanase, to Fleming (3) who in 1929 first described the antibacterial properties of penicillin, to Florey and his associates (usually referred to as the Oxford Group), who in 1940 reported on its chemotherapeutic action in animals (4) and in the following year on its clinical use (5), and to Dubos (6) who in 1939 discovered tyrothricin, an antibiotic agent with a high degree of activity against gram-positive pathogens, but too toxic for parenteral administration. The discovery of tyrothricin, while only of limited practical value, was nevertheless of far reaching significance, because it made investigators all over the world fully "antibiotic conscious" and stimulated a systematic search for other agents of this type, which still is in the ascendancy. To date, more than 100 antibiotics have been isolated and studied, but only two, penicillin and streptomycin, have been outstandingly successful, one of them,

penicillin, being the first chemotherapeutic agent in medical history, which completely fulfills Ehrlich's requirements to be entirely free from toxicity for the host and yet fully effective against pathogenic organisms.

Although penicillin was discovered in 1929, more than 10 years elapsed before it was first tried *in vivo* and it could not have acquired practical significance in war medicine had it not been for the vision of an American pharmacologist, Alfred Newton Richards, for the combined efforts of American and British scientists in governmental, academic and industrial laboratories and for the skill, ingenuity and efficiency of the American industry.

Even the best drug is of no use unless it is obtainable in the quantities needed and at a cost which comes within economic reach. The first demonstration of the clinical value of penicillin in 1941 required approximately 100 liters of the mold brew to provide enough penicillin for the treatment of 1 patient for 1 day, and in order to waste as little as possible of the precious material, the urine of the treated patients was collected for the extraction and re-purification of the excreted drug. The enormous progress made since that time becomes immediately apparent upon inspection of a chart illustrating the changes in cost and production since 1943, the first year of large scale commercial operation (fig. 1). During these two years the price for 100,000 units of penicillin declined from 20 dollars to 60 cents, while the production increased from 0.15 billion units during the first quarter of 1943 to 1980 billion units during the last quarter of 1945. This amazing reduction in cost has been achieved partly by the replacement of the original flask production method with a deep fermentation process, partly by improved chemical extraction methods and particularly by the discovery of new penicillin mutants and strains which increased the yields more than 100-fold.

Due to the fact, that even the original low potency concentrates of penicillin were practically nontoxic, only little pharmacological research was

needed before large scale clinical use of the new drug could be started. No such easy course however was possible with streptomycin, an antibiotic discovered (7), first produced and tested (8) pharmacologically studied (9) and clinically used (10) in this country and already recognized as the worthy counterpart of penicillin in the gram negative field. Although this agent has a far greater safety margin than the sulfonamides or the older chemotherapeutic drugs, it nevertheless possesses defi-

of these two drugs and draw your attention to some of the pharmacological problems, which are common to all antibiotics and which are perhaps not always sufficiently realized. Among them are (1) the great variations in pharmacological and toxicological properties of samples with equal chemotherapeutic potency and (2) the problem of acquired resistance to the drug, the so called "fastness."

The great qualitative variations in the pharma

TABLE 1

Susceptibility of pathogens to chemotherapeutic agents upon parenteral administration (excluding serum therapy)

+++ Nearly always effective

++ Often effective

+ Occasionally effective

- Not effective

	IN VITRO			ANIMALS			MAN		
	1935	1941	1946	1935	1941	1946	1935	1941	1946
<i>Staph aureus</i>	+	++	+++	+	++	+++	+	+	+++
<i>Strep hemolyticus</i>	+	++	+++	+	+++	+++	+	++	+++
<i>Strep viridans</i>	+	+	+++	-	+	++	-	+	++
<i>Neisseria intracellulans (Meningococcus)</i>	+	+	+++	-	+	++	-	++	++
<i>Neisseria gonorrhoeae</i>	+	+++	+++	+	+++	+++	+	+++	+++
<i>D pneumoniae</i>	+	+++	+++	-	+	+++	-	++	++
<i>K pneumoniae (Friedlander's bacillus)</i>	+	+	+++	-	+	+++	-	+	++
<i>Cl welchii</i>	+	+	++	+	++	++	+	++	++
<i>Cl oedematis</i>	+	+	++	+	+	++	+	++	++
<i>Hemophilus influenzae</i>	+	+	+++	-	-	++	-	+	++
<i>Hemophilus pertussis</i>	+	+	+++	-	-	++	-	+	++
<i>B proteus</i>	+	+	+++	-	+	++	-	+	++
<i>P aeruginosa</i>	+	+	+++	+	+	++	-	+	++
<i>Pasteurella tularensis</i>	+	+	+++	-	-	+++	-	-	+++
<i>Brucella abortus</i>	+	+	+++	-	-	++	-	+	++
<i>Brucella suis</i>	+	+	++	-	-	+	-	-	+
<i>E coli</i>	+	+	+++	-	+	++	-	+	++
<i>Salmonella paratyphi</i>	+	+	+++	-	++	+++	-	+	+
<i>Salmonella schottmülleri</i>	+	+	+++	-	++	+++	-	+	+
<i>Shigella paradyenteriae (Flexner)</i>	+	++	+++	-	++	++	-	-	+
<i>Mycobacter tuberculosis</i>	+	+	+++	-	+	++	-	-	+
<i>B anthracis</i>	+	+	+++	-	-	+++	-	+	+++
<i>Treponema pallidum</i>	++	++	+++	++	++	+++	++	++	+++
<i>Leptospira icterohaemorrhagiae (Weil's disease)</i>	++	++	+++	-	+	+++	-	-	+++
<i>Plasmodium falciparum</i>				+++	+++	+++	+++	+++	+++
<i>Plasmodium vivax</i>				++	++	++	++	++	++
<i>Trypanosoma gambiense</i>	++	++	++	++	+++	+++	++	++	++
<i>Endamoeba histolytica</i>	++	++	++	++	++	++	++	++	++
<i>Lymphogranuloma venereum</i>				-	++	++	-	++	+++

Average response of 29 infectious diseases to chemotherapeutic agents in man

Often effective

15% 36% 73%

Nearly always effective

3% 9% 27%

Since the appraisal of the effectiveness of chemotherapeutic agents in specific diseases is by necessity arbitrary, the above table is primarily intended to illustrate a general trend.

nite toxic properties. It is a credit to American pharmacology, that less than 2 years after its discovery sufficient pharmacological and toxicological data could be accumulated to permit not only extensive clinical investigations, but also the establishment of official standards.

Since you undoubtedly are familiar with some of the review articles (11, 12) on penicillin and streptomycin, I should like to dispense with a discussion of the general pharmacological properties

of these two drugs and draw your attention to some of the pharmacological problems, which are common to all antibiotics and which are perhaps not always sufficiently realized. Among them are (1) the great variations in pharmacological and toxicological properties of samples with equal chemotherapeutic potency and (2) the problem of acquired resistance to the drug, the so called "fastness."

The great qualitative variations in the pharma

equally effective doses of antibiotics will undoubtedly lead to conflicting pharmacological and clinical reports because investigators may fail to realize, that the term X milligrams or Y units means little, unless additional microbiological and pharmacological data and preferably the source and lot number of the product are known. Statements of the dose in terms of a recognized biological unit together with that of the cation form-

ing the salt are generally regarded as sufficiently complete. However, while this assumption is correct with most galenic preparations, it is definitely not valid for antibiotics which are produced by living organisms and are subject to the many variations, that are likely to accompany metabolic processes. Not only is the nature of the strain of the parent mold or bacterium likely to influence the end product, as evidenced by the chemically and biologically different penicillins I, G, K and X, but also the type of medium, the age of the culture upon harvesting, the occurrence of mutants, the type of cultivation (surface or submerged),

actinomycetes and bacteria for the production of our antibiotics, instead of being able to prepare them synthetically. Only then will a dose stated in terms of weight convey all the information needed, up to that happy day, however, it will remain the task of the pharmacologist to find for each new antibiotic a sufficient number of pharmacological characteristics adaptable to the purposes of bioassay and to apply such assays to each and every lot. While the routine performance of such tests will usually be left to technicians, the selection of the most characteristic, constant and sensitive pharmacological criteria obviously depends upon a thorough pharmacological analysis and hence belongs clearly in the field of pharmacological research.

The development of bioassays for antibiotics is complicated by the fact, that the procedure usually observed in the investigation of a new drug, viz. to conduct the entire study with material derived from the same batch, cannot be used with antibiotics, since no two batches may be expected to be qualitatively completely alike. Only by the careful study of a large number of different batches is it possible to notice the constantly recurring properties and to base upon them standards, which will assure a qualitatively, as well as quantitatively well defined product.

To prove these remarks, I should like to dwell briefly upon the wide variations in clinical side reactions found in the administration of the same number of units of different lots of penicillin or streptomycin.

Chemists are well aware that the pain frequently following the intramuscular injection of these drugs greatly varies in the same patient with different batches of the material. Herwick, et al. (13) have shown that with penicillin the degree of local irritation is directly related to the purity of the preparation. Likewise, Silvers (14) was able to demonstrate that the dermatitis observed after the injection of an impure penicillin failed to occur in the same patient when pure penicillin was used.

In animals, the acute toxicity of penicillin not only varies with the type of cation, being least with the Na and greatest with the K salt (15, 16), but also greatly depends upon the purity of the preparation (17, 18) (fig. 2) the intravenous L D 50 of pure Na penicillin G being 3.2 million Oxford units per kgm. mouse, while the corresponding figure for an impure preparation is 60,000 Oxford units per kgm. An even greater variation is found with streptomycin preparations of different purity (19) (fig. 3). While variations in lots of different potency and thus different bulk content might be expected, it is more difficult to understand why preparations of approximately the same potency should show an almost equally wide range in the

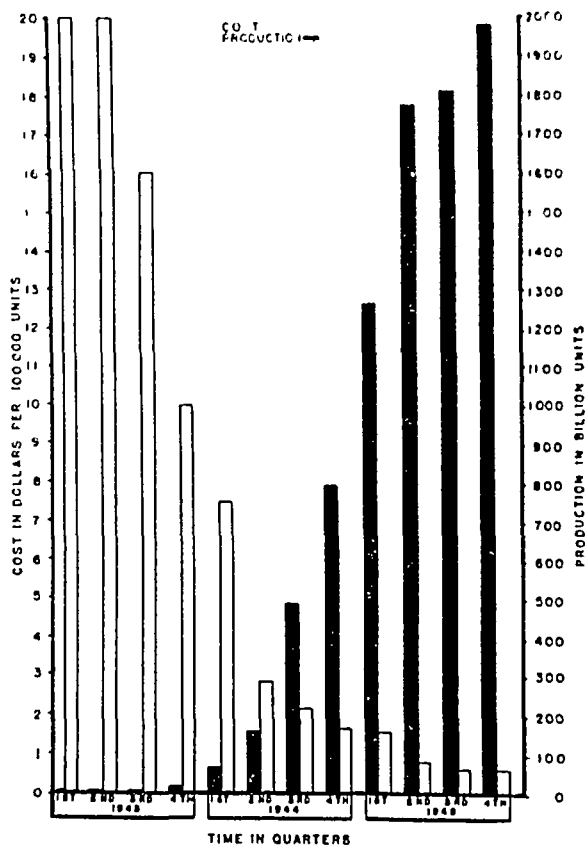


Fig. 1 Trends in production and cost of penicillin, 1943-1945

and, of course, the chemical methods used for extraction, concentration and purification. All these factors may, and often do, influence the final product qualitatively as well as quantitatively. Standardization of the parent strains and manufacturing techniques reduce the likelihood of qualitative changes, there will, however, always remain some uncontrollable factors which may exert a far-reaching influence upon the toxicological and pharmacological properties of the final product without interfering with its antibacterial activity and hence unrecognizable by a potency assay. These facts are depressing, but will have to be faced as long as we have to depend upon fungi,

intravenous and subcutaneous toxicity, particularly if the potency of these lots comes close to that of the pure material. Varying amounts of bulk, differences in the speed of absorption from the subcutaneous tissues and the presence of some highly active, unidentified impurities may account for these findings.

In addition to quantitative variations in the acute toxicity, there are qualitative differences

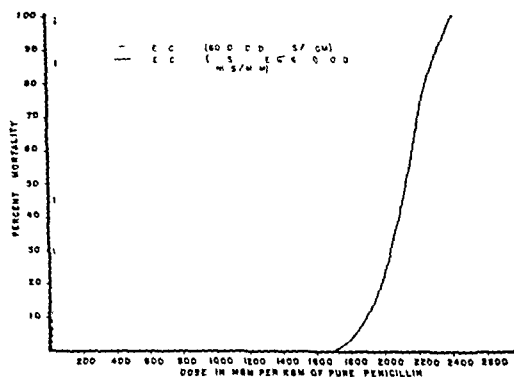


Fig 2 Acute intravenous toxicity of penicillin

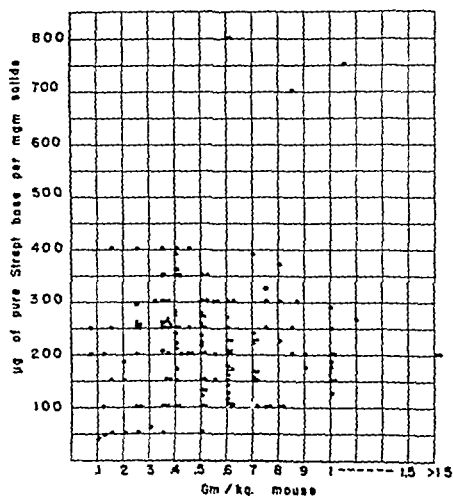


Fig 3 Variations in the acute subcutaneous toxicity of streptomycin in mice. Each point represents the LD 50 of a different lot.

between individual batches of penicillin or streptomycin. Thus, Garrod (20) observed that within certain limits the bactericidal effect *in vitro* of commercial penicillin was greater at lower than at higher concentrations, this anomalous behavior disappeared when pure penicillin was used. Other qualitative differences in the chemotherapeutic properties of penicillin samples of different purity were noted by Dunham and Rake (21) who found impure concentrates more active against *T. palli*

than crystalline penicillin G, which was almost devoid of such activity. In experiments conducted by Graessle and Bugie (22) in our laboratory on the *in vitro* activity of various lots of penicillin against *Dirofilaria immitis* (table 2) low potency preparations killed the microfilaria, while crystalline penicillin G was ineffective in this respect, except in concentrations, which produced damage through unspecific osmotic changes.

Streptomycin batches of varying purity and different methods of manufacture exhibit even more striking pharmacologic differences. In the early stages of the investigation of this antibiotic it was noted (17) that intravenous injection of certain lots produced in rats, cats and dogs a steep fall of the arterial blood pressure while in rabbits the same lots raised the blood pressure (fig. 4). There

TABLE 2

In vitro activity of various lots of penicillin against the microfilariae of *Dirofilaria immitis*
24 hour results

COMPOUND	MG/M. /CC				
	2	4	8	16	32
Crystalline Penicillin 1667 Units/Mg Units/cc	Alive 3 331	Alive 6 663	Alive 13 336	Alive 26 672	Dead 53 344
Na Penicillin 429 Units/Mg Units/cc	Alive 558	Alive 1 716	Dead 3 432	Dead 6 864	Dead 13 728
Ca Penicillin 111 Units/Mg Units/cc	Alive 222	Alive 444	Dead 888	Dead 1 776	
5R8261 Penicillin Impurities No activity	Alive 0	Alive 0	Dead 0	Dead 0	Dead 0
NaCl			Alive	Alive	Dead

also were found peripheral vasodilatation, constriction of the isolated intestines and uterus stimulation of gastric secretion and a temporary inhibition of the water diuresis. These reactions suggested to us the presence of a histamine-like impurity, an assumption which was fully confirmed, when treatment of highly contaminated samples with histaminase resulted in the complete removal of the various histamine type reactions (fig. 5). Various lots varied greatly in their histamine effect and in occasional lot was even completely free from it (fig. 6).

Through close cooperation with clinical investigators it was possible to link the presence of an excessive amount of the histamine like impurity to a variety of side reactions in patients such as headache, flushing of the face, nausea, vomiting and occasional fainting spells (fig. 7).

The histamine-like factor, which now has only historical interest, since it is removed from streptomycin lots of recent manufacture, is only one of the pharmacodynamically highly active impurities, the others being responsible for the acute intravenous and subcutaneous toxicity and perhaps some of the clinical side reactions. This impurity is not influenced by histaminase (fig 5), it appears to be an entity by itself and distinct from streptomycin, since, as mentioned before, even the most

temperature pain in the joints or skin rashes is due to streptomycin itself or one of its impurities or should be attributed to an abnormal sensitivity or sensitization of the patient.

The data rather sketchily presented in the foregoing may serve as proof that the clinical use of

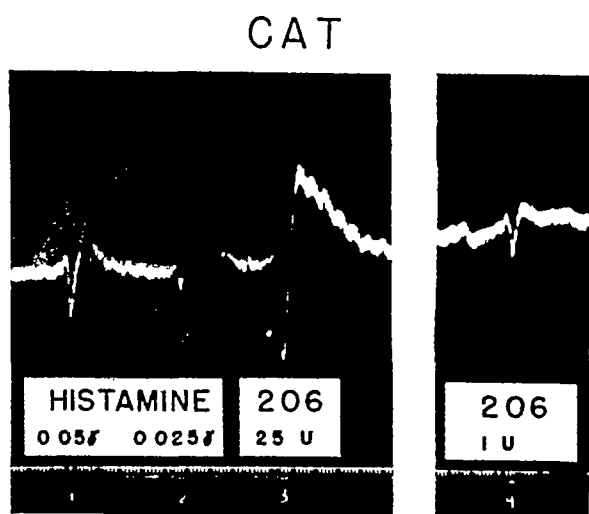
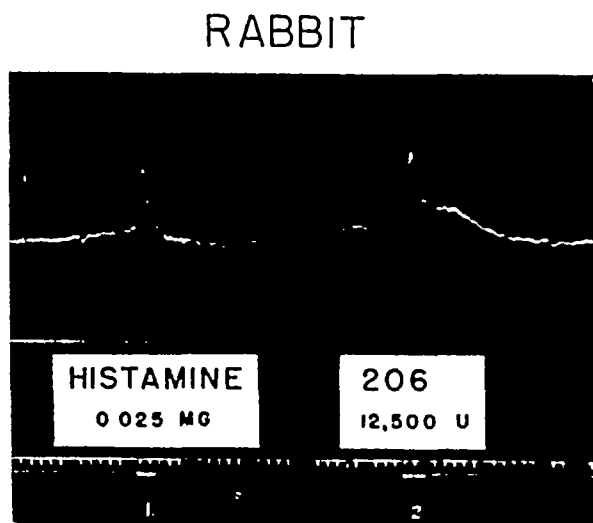


Fig 4 Comparison of blood pressure effect of impure streptomycin in the rabbit and the cat

highly purified lots vary in their intravenous and subcutaneous toxicity.

It has not yet been possible to establish a correlation between a high acute toxicity in animals and the suitability of a particular batch for clinical use, nor could it be determined whether the neurotoxic signs occasionally following prolonged administration of streptomycin are an intrinsic property of this antibiotic or are due to an impurity, and whether the occasional occurrence of elevated

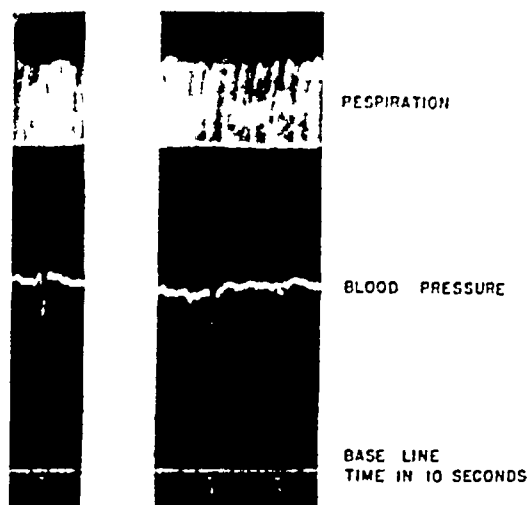


Fig 5 Effect of histaminase treatment on depressor effect of impure streptomycin

Cat 3.25 kg, nembutal anesthesia 35 mg/kg subcutaneously. 1 Histamine hydrochloride 0.00005 mg/kg. 2 Streptomycin concentrate, lot 206, 50 units/kg. 3 Streptomycin concentrate, lot 206, histaminase treated 50 units/kg.

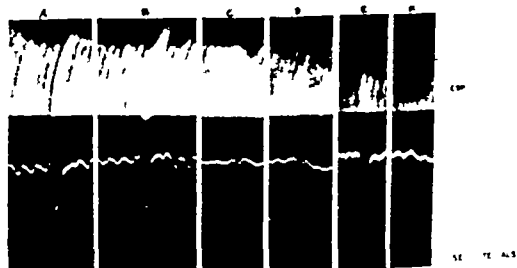


Fig 6 Comparison of the depressor effect of 4 different lots of streptomycin

Cat, wt 3.43 kg, nembutal, 30 mgm/kg I.P. A, 0.01 mgm histamine phosphate. B, 5000 Units/kgm of streptomycin lot 169. C, 5000 Units/kgm of streptomycin lot 162. D, 10,000 Units/kgm of streptomycin lot 162. E, 10,000 Units/kgm of streptomycin lot 5R8798. F, 10,000 Units/kgm of streptomycin lot 5R8869.

some of the most promising antibiotic agents would be impossible without extensive pharmacological research and constant quality control through pharmacological tests based on this research. This, however, is only part of the contribution, which pharmacologists may render to the new chemotherapeutic agents, of equal, although

less immediate importance is research on the problem of drug fastness, which threatens the future use of these drugs.

The phenomenon of changed susceptibility to the repeated administration of a drug is not new. It may manifest itself in the need for an increase or decrease of the original dose as well as in a qualitatively different type of reaction. Alterations in

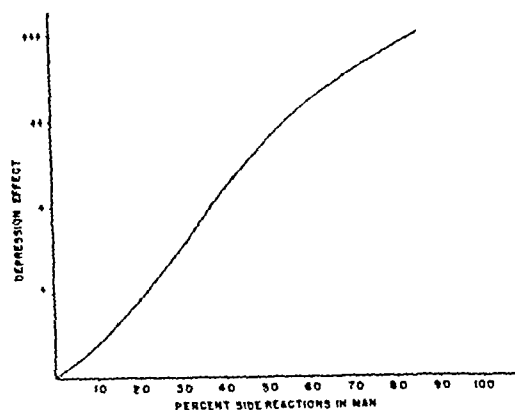


Fig 7 Correlation between clinical side reactions and effect on blood pressure (56 lots streptomycin)

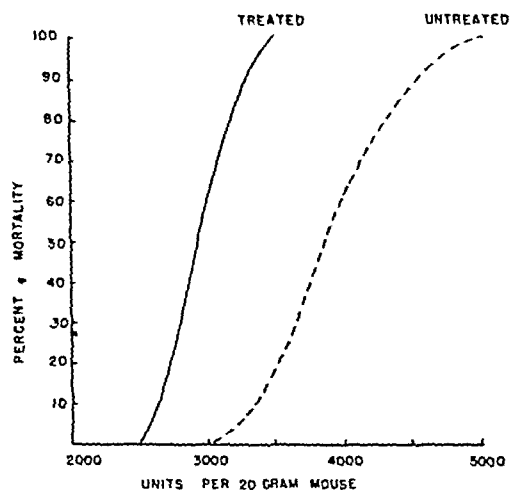


Fig 8 Intravenous toxicity of histaminase treated streptomycin concentrate

the absorption, excretion, detoxification and metabolic disposal of the drug, as well as the development of allergic phenomena are some of the reasons, which may necessitate a change in the dosage schedule of morphine, barbiturates, arsenicals, etc. A decrease in the susceptibility of pathogenic organisms to a chemotherapeutic agent is likewise a well known occurrence and quinine or arsenic-resistant strains have often interfered with the

use of these otherwise highly effective drugs. However, the development of drug fastness has never become so alarming as since the introduction of the sulfonamides and the antibiotics. Whether the high incidence of drug fastness is due to the liberal and indiscriminate use of these new, practically non-toxic agents or whether these drugs are particularly likely to produce resistant strains, is not known. Regardless of the cause, however, there is the prospect that in the relatively near future penicillin and streptomycin may to a considerable degree lose their usefulness in the therapy of some of the most prevalent infections unless some means can be devised to restore the original susceptibility of either host or pathogenic agent.

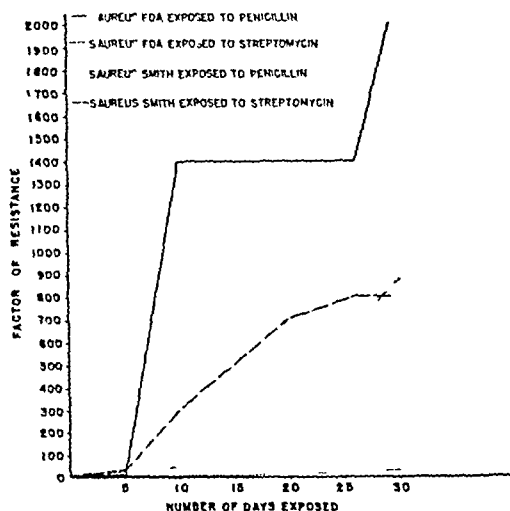


Fig 9 Acquired resistance of *Staphylococcus aureus* strains to penicillin and streptomycin *in vitro*

An increased resistance to antibiotic agents can probably be developed by almost all types of pathogenic organisms, including *Mycobacterium tuberculosis* (23, 24). It varies widely, however, even with closely related strains, and appears with different antibiotics to a different extent and with different speeds (fig 9). Drug fastness can be produced *in vitro* as well as *in vivo* (25). Whether a strain rendered drug-resistant by cultivation in a medium containing increasing concentrations of the chemotherapeutic agent will lose its fastness through repeated transfers to normal culture media or through animal passages cannot be answered summarily. Todd, et al (26) have found that staphylococci which have become resistant to penicillin lose their fastness upon subculture in normal broth and become again susceptible to penicillin concentrations which can easily be obtained in the human body. Experiments in our labora-

toxy (27) have shown a similar behavior for *L. coli* while streptomycin resistant *L. typhi* and *S. schottmulleri* retained their fastness for more than three months. Similar observations on streptomycin fast gonococci and meningococci have been published by Miller and Bohnhoff (28). It appears, that naturally resistant strains retain this characteristic to a far greater degree than strains that have acquired resistance only through culture in media containing increasing concentrations of the antibiotic (29). Unfortunately, however, the incidence of naturally resistant strains appears to be quite high (30, 31, 32) and it is likely to increase as the less resistant strains are gradually eliminated and only the most resistant strains survive (33).

The question naturally arises what measures can be taken to counteract the development of drug resistance. One of the most effective ways appears to be the selection of a dose sufficiently large to rapidly eliminate the pathogenic organisms. In view of the low toxicity of penicillin and streptomycin, which permits the administration of doses far in excess of those required to stop bacterial growth, such a course can readily be followed, particularly if the resistance of the specific pathogen is determined prior to, or simultaneously with, the start of the treatment. The desirability of obtaining high initial concentrations of the antibiotic makes it particularly important to insist on a dosage regime, which insures the maintenance of high blood concentrations. The use in the treatment of systemic infections of such preparations as salves, lozenges, chewing gum, sprays, etc. which are likely to produce adequate concentrations only at the immediate site of application would therefore appear to create a definite hazard unless special forms can be developed, which will assure a completely adequate drug concentration in blood and body tissues.

Another measure which may be worthy of investigation, is the combination of different chemotherapeutic agents, as suggested by Carpenter, et al. (34), who observed *in vitro* that 5 different strains of gonococcus failed to develop resistance, when exposed to the combined action of sulfathiazole, promin, rivanol and penicillin, although they regularly developed fastness if exposed to only one of these agents. This course, however, might have a number of serious drawbacks, since it exposes the patient to the toxic and antigenic effects not only of one, but several drugs.

Once drug fastness has been developed, a change in the chemotherapeutic agent is at this time the only means for continuation of an effective treatment. Unlike the sulfonamides of which each individual member is capable of producing resistance against the entire group (35), there seems to be no such interchangeability between sulfonamides and antibiotics, or, as a rule, between dif-

ferent antibiotic agents. Powell and Jamieson (36) and McKee and Rake (37) found that sulfonamide fast pneumococci remained susceptible to penicillin and experiments in our laboratory have shown that in exposure of *L. coli* to streptomycin failed to induce resistance to streptomycin or vice versa; indeed, a streptomycin fast salmonella strain has been successfully used to detect minute amounts of streptomycin in a mixture of these two closely related antibiotics (38). Similarly, a streptomycin fast *Staph. aureus* strain failed to show resistance against penicillin and Miller and Bohnhoff (28) have reported that streptomycin fast gonococci and meningococci remained susceptible to penicillin. However, Waksman (39) reported that a streptomycin resistant *P. vulgaris* became also resistant to streptomycin and unpublished experiments by Grassle and Irost from our laboratory have indicated that penicillin resistant strains of *Staphylococcus aureus* may occasionally increase in their resistance to streptomycin by as much as 30 times.

If a change of the chemotherapeutic agent should remain the only way of overcoming in already established drug resistance, many new antibiotics may have to be developed if medicine is to continue to enjoy the advanced stage of chemotherapy which has been achieved in the last 5 years. There is, however, the possibility that pharmacological research may find other means of retarding or preventing the development of drug resistance. Thus, Schwartzman (40) observed that certain amino acids may greatly alter the bactericidal action of penicillin, methionine and penicillin together exert a synergistic inhibitory effect upon *E. coli*, which normally is markedly resistant against penicillin, and mixtures of serum and methionine, which themselves produce only incomplete inhibition, were capable of increasing the susceptibility to penicillin by as many as 12-36 times (40). Similarly, addition of methionine, methionine sulfoxide and threonine greatly enhanced the penicillin susceptibility of *Brucella*, *Eberthella*, *Salmonella* and *Shigella*, whereas other amino acids (aspartic, glutamic, hydroxyglutamic, asparagine, cystine, arginine, histidine and hydroxyproline) were capable of suppressing the effect of penicillin upon gram-negative organisms. Although these studies were performed *in vitro* only and have no direct bearing on the phenomenon of drug fastness, there is nevertheless a constantly growing evidence of the interrelationship between the nutritional state of the host, susceptibility to infection, immunological reaction and response to pharmacological agents (41, 42). Deficiency of certain vitamins has been found to either enhance or decrease the susceptibility to infections (43, 44) and some of the so-called "antivitamin" possess definite, though moderate

chemotherapeutic properties. The antirickettsial activity of para-aminobenzoic acid also belongs here. It may therefore be possible to influence the development or the duration of drug resistance by dietary means or through direct pharmacodynamic action upon metabolic processes. To deal with this problem successfully will require much pharmacologic research on the mode and site of action of antibiotics and on the general problem of interrelationship between susceptibility to infection, efficacy of chemotherapeutic agents and state of metabolic activity.

There can be little doubt, that the advances in bacterial chemotherapy could not have proceeded without the help of experimental pharmacology. Pharmacology itself, however, has greatly been benefitted by the study of these agents, which have brought about a far reaching change in the technique of selecting an optimal dose for the individual patient. While it has long been known that "Corpora non agunt nisi soluta" and that no drug can be effective unless present at its specific site of action, it was not until 1937, when Marshall stressed the need of knowing the sulfonamide concentration in the blood, that the principle of adjusting the dose to the required blood levels has become universally accepted, not only for the sulfonamides, but also for other drugs.

Another measure of similar importance has come into wide use with the advent of the antibiotics, although again its principle was previously well known. Under the stress of conserving the first in adequate supplies of penicillin and streptomycin, as well as in order to obtain complete data on their chemotherapeutic efficiency in man, it became an established routine to determine *in vitro* the sensitivity of the pathogen to the drug and to establish by means of blood concentration tests in the individual patient a dose that would assure an effective concentration. Two principles have thus been introduced, which might well be more generally adopted. First, to determine in the individual patient the extent of his actual need for a particular drug and second, to make sure, by means of suitable assay methods, that this requirement is being met. This is a far cry from the old procedure of selecting the dose from experience or from books, yet it is not only scientifically sound, but indispensable with drugs such as penicillin and streptomycin which may rapidly produce drug resistance, if given in suboptimal amounts. The advent of the new chemotherapeutic agents has thus not only provided the medical profession with weapons of hitherto unknown power, but has also taught us more rational and effective principles of selecting and administering therapeutic agents.

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DONALD RUSSELL HOOKER

This September number of Federation Proceedings has been issued under the guiding hand of the man whose dreams, plans and effort have made the publication possible. Even through several months of serious illness, Dr. Donald Russell Hooker has carried his work ably to a close.

On August 1, 1946, Doctor Hooker died at the Johns Hopkins Hospital. As the first permanent Secretary and as Managing Editor of the Proceedings, Doctor Hooker gave freely to the Federation the full measure of his excellent administrative ability, scientific and editorial judgment. He will be very greatly missed as friend, humanitarian, and for his generous, skillful and widespread contributions to the cause of science.

With this brief note, members of the Federation wish to extend their deep appreciation and sympathy to Doctor Hooker's family. So great a loss can be more fittingly recognized at a later date.

REPORTS SUBMITTED BY SECRETARIES OF THE CONSTITUENT SOCIETIES

AMERICAN PHYSIOLOGICAL SOCIETY

The annual meeting of the American Physiological Society for 1946 was held in Atlantic City, New Jersey on March 11 through March 16. Meetings of the Council of the Society were held on March 10, 11, 12 and 14.

The Society adopted an amended constitution, a copy of which will be published in another issue of the Federation Proceedings. The Society elected to membership all of the nominees approved by the Council during the years 1943, 1944 and 1945. It also elected to membership all of the nominations approved by the Council in 1946 including six honorary members as follows: Professors August Krogh, Copenhagen, L. Orbeli, Moscow, Joseph Barcroft, Cambridge, A. V. Hill, London, E. D. Adrian, Cambridge, L. Lapicque, Paris.

The Society approved the following appointments: Dr. Homer Smith to the Board of Publication Trustees for the 1944-47 term, Dr. Frank C. Mann for the 1945-48 term, and Dr. A. C. Ivy for the 1946-49 term. Dr. Ivy was named Chairman of the Board of Publication Trustees.

The Society passed unanimously the following resolution:

"Whereas, Dr. Walter J. Meek has served the American Physiological Society as Chairman of the Board of Publication Trustees since its creation, and by his devoted work has been responsible to a major extent for the high quality and financial success of the publications of the Society:

"Therefore, be it resolved, that the members of the Physiological Society extend to Dr. Meek their sincere thanks for his generous and large services."

The Society was informed of the resignation of Dr. D. R. Hooker as Secretary of the Federation of American Societies for Experimental Biology. In recognition of his long and valuable services the American Physiological Society formally thanked Dr. Hooker for what Professor A. J. Carlson called "the tremendously valuable, unselfish work that Dr. Hooker has done for our group during the last thirty years." The motion was passed by a unanimous standing vote.

The Society approved the recommendation of the Council endorsing the work of the National Society for Medical Research and instructed the treasurer to include with the next statement of annual dues an invitation to contribute to its fi-

nanacial support from the treasurer of the American Physiological Society.

The American Physiological Society was confronted at its 1946 meeting with the issue of military censorship of scientific information. Upon unanimous vote the following resolution was sent to the President:

"President Harry S. Truman
White House
Washington, D. C.

The members of the American Physiological Society are profoundly disturbed by the continuation of rigid secrecy orders covering scientific research in biological and medical problems. It is our considered opinion that it is not in the public interest to continue to permit military censors to determine what facts may or may not be disclosed to other scientists or to the public in any cases other than those directly involving military weapons. It is further our belief that in any future program of government financed research, by civilian scientists on problems other than those dealing with military weapons, the principle of freedom of research and publication should be scrupulously preserved against military domination.

Signed for the American Physiology Society
by its major officers"

The Council authorized the appointment of Drs. A. C. Ivy and E. Shorr as members of the Federation Committee for the Protection of Medical Research.

The Society received the report of the Survey Committee, Dr. E. F. Adolph, Chairman, Drs. T. E. Boyd, J. H. Comroe and Philip Dow. Portions of this report will be published by the Committee.

Tentative plans were made for the next annual meeting in Chicago in the week beginning May 18, 1947.

A committee was appointed with Dr. R. W. Gerard as chairman to organize for the 1947 meeting a symposium on the training of physiologists, and to explore the possibilities for the extension of physiological instruction into wider areas.

The following officers were elected: Dr. Wallace O. Fenn, President, Dr. Maurice B. Visscher, Secretary, Dr. D. B. Dill, Treasurer, and Dr. H. C. Bazett, Councilor.

AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS

At the Atlantic City Meeting the following Officers were elected to take office July 1

A B Hastings—President

H T Clarke—Vice President

O A Bessey—Secretary

G O Burr—Treasurer

A K Balls—Councilor-at-large

W C Rose was elected Chairman of the Nominating Committee

The reports of the Treasurer, Finance Committee, Editorial Committee and other Committees were read and approved. H B Lewis discussed the work of the Placement Service and agreed to remain in charge of it for another year.

Among the other actions taken, it was voted to set the annual dues at \$3.50 because of the increased cost of the Federation Proceedings. Furthermore, the Society expressed its hearty

endorsement of the purposes of the National Society for Medical Research and instructed the Treasurer to include with the statement of the next annual dues an invitation to each member to contribute to that organization. The Treasurer was authorized to receive and pay over such contributions.

The President made the following new appointments: A Committee on the Professional Training of Biological Chemists, H B Lewis, Chairman, W M Clark, E A Doisy, V du Vigneaud and C A Elvehjem, Committee on Clinical Chemistry, V C Myers, Chairman, D D Van Slyke, H T Clarke, Historian of the Society, P A Shaffer to succeed R H Chittenden, deceased.

Eighty-three persons were recommended by the Council as eligible and endorsed for membership and were duly elected members.

AMERICAN SOCIETY FOR EXPERIMENTAL PATHOLOGY

OFFICERS AND COMMITTEES

Officers for the Year 1946-47 President, Paul R Cannon, Vice-President, Douglas H Sprunt, Secretary-Treasurer, Frieda S Robschert-Robbins, Councilors, H P Smith and John G Kidd, Representative in the Division of Medical Sciences of the National Research Council, H P Smith, Representatives on the Council of the American Association for the Advancement of Science, Malcolm H Soule and E B Krumbhaar, Representative on the Council of the Union of American Biological Societies, H P Smith, Representatives on the Eli Lilly Award Committee (jointly with the Society of American Bacteriologists) For Nominations Morton McCutcheon, For Award Shields Warren.

New Members Doctors Allen B Eschenbrenner, Joseph John Lahch, George Rodney Meneely and Albert Segaloff.

In accord with the recommendation of the Council sympathetic support to the newly formed

National Society for Medical Research was voted and the suggestion made that members contribute financially as individuals. The President outlined the need for additional funds in accord with the action taken by the Council in order to give more adequate financial support to the office of the Federation Secretary and to provide for adequate funds for the operation of the Society itself. This action was approved and it was voted to increase annual dues to three dollars per year. The President of the Association of American Pathologists and Bacteriologists was informed that our membership would welcome arrangements whereby members could more conveniently attend the annual meeting of the Association and of the Society for Experimental Pathology. It is hoped that in the future the Association might be able to meet immediately ahead of the Federation either in the same city or in a city near by.

The Society accepted with regret the resignation of Dr Rufus Cole, Member Emeritus of the Rockefeller Institute for Medical Research.

THE AMERICAN INSTITUTE OF NUTRITION

The tenth annual meeting of the American Institute of Nutrition was held in Atlantic City, March 11-15, 1946. Since the annual meetings were suspended during the war period this was the first meeting since 1942.

Council Meetings Council meetings were held at the Ambassador Hotel, Monday, March 11, at 3:00 P. M. and at 7:30 P. M. All members were present. Formal actions of the Council are reported in the minutes of the business session.

Scientific Sessions The scientific program consisted of one symposium and four half-day sessions of scientific papers grouped according to topic. The symposium was entitled, "The application of the newer knowledge of nutrition to present-day problems" and the five speakers (R. M. Wilder, L. A. Maynard, W. E. Krauss, P. C. Jeans, and C. A. Elvehjem) discussed various aspects of the wartime activities of the Food and Nutrition Board. Dr. W. C. Rose, President, acted as chairman and made a few introductory remarks.

Dr. A. H. Smith presided at the Tuesday afternoon session, Dr. H. B. Lewis at the Wednesday morning session, Dr. H. A. Mattill at the Wednesday afternoon session, and Dr. W. C. Rose at the Thursday morning session.

A total of 37 papers was presented and 18 were read by title. A great deal of interest was displayed in the nutrition program necessitating securing a larger room. The estimated attendance at the various sessions ran from 250 to 400.

Business Sessions Two business meetings were held, one at 7:30 Tuesday, March 12, and the other at 10:00 A. M. Thursday, March 14. The business meetings were presided over by the President, W. C. Rose.

Tuesday, March 12, 7:30 The report of the Treasurer was read by Dr. E. M. Nelson. The auditors, Dr. J. H. Roe and Dr. D. B. Jones, previously appointed by the President, had examined the Treasurer's books and found them correct. The report of the Treasurer was accepted and approved.

Dr. George Cowgill, Editor of the *JOURNAL OF NUTRITION*, reported that during the year 1945 volumes 29 and 30 of the *JOURNAL OF NUTRITION* were published, they contained 102 papers. There were submitted during the year 163 articles. The average number of papers printed per issue in volumes 29 and 30 was 8.5, the same as for the previous year. The average number of pages per article proved to be 9.0 compared with 9.4 for 1944.

During the two years 1944 and 1945 the format of the Journal was one carrying more printing per page and representing an adjustment to the paper shortage created by the war. Beginning with Jan-

uary, 1946, Wistar Institute returned to the older format for all of its journals. At the same time, in response to a request from the Editor, it increased the size of the *JOURNAL OF NUTRITION* from the old 100 pages per issue (600 per volume) to 120 pages per issue (720 per volume). This represents an increase of 20 per cent in the size of the Journal, which should help to secure more prompt publication of accepted papers. This change was made without any increase in cost of the *JOURNAL* to subscribers.

In accordance with past policy, a change was made in the picture of a distinguished scientist printed on the front cover of the Journal beginning with the issue for January, 1946. The new picture chosen by the Editorial Board was that of Russell H. Chittenden.

During the year 1945 efforts were made to find some way for honoring Dr. John R. Murlin, who, more than any other single person, did most to establish the *JOURNAL OF NUTRITION* and the American Institute of Nutrition. Dr. Murlin had retired from his post at the University of Rochester on account of age, but because of the war and a shortage of personnel, had been requested by his university to continue for another year. This period expired in June, 1945. It seemed particularly appropriate, therefore, that something to honor him be done as soon as possible after that date. Plans were finally completed for designating volume 31 (January-June, 1946) as the *JOHN R. MURLIN HONOR VOLUME*. Each issue of this volume was to carry on its front cover such a title. In the first issue there appeared a photograph of Dr. Murlin which thus serves as a frontispiece for the volume. The picture was accompanied by an article of appreciation written by a pupil and younger associate, Dr. E. S. Nasset.

During 1945 printing shop difficulties at the Wistar Institute operated again to delay final appearance of the issues of the *JOURNAL*. This represented continuation of an old problem which was mentioned in previous reports. The present prospects are that this will continue for some time at least, but that Wistar Institute will succeed gradually in returning to the correct printing schedule for all of its periodicals.

Dr. Cowgill's report was accepted and approved. The President outlined to the members the necessity for increasing Federation dues from \$1 to \$2 in order to meet the increased operating expenses of the Federation with the advent of a new Secretary. This would involve increasing the Institute dues from \$2 to \$3 for 1946. It was moved and carried that this be done.

The Secretary reported that the Council had ap-

proved the appointment of Dr. Walter Russell to replace Dr. Maynard as the representative of the Institute on the Division of Biology and Agriculture of the National Research Council. This recommendation was approved.

The report of the Placement Service by H. B. Lewis was approved as was the continuation of Dr. A. H. Smith as the representative of the Institute on the Editorial Board of *FEDERATION PROCEEDINGS*.

The Secretary announced that the reports of the Borden and Mead Johnson Award Committees and the report of the Nominating Committee had been approved by the Council and that the report of the Nominating Committee would be presented at the Thursday morning business meeting. Dr. Rose pointed out that since the Thursday morning business meeting would be restricted to members of the Institute only, the presentation of the Borden Award and the Mead Johnson Prize would be made immediately following the scientific session on Thursday morning and preceding the business meeting. Dr. Rose appointed Dr. I. S. Kleiner and Dr. H. H. Williams as tellers.

Thursday, March 10 The tellers, I. S. Kleiner and H. H. Williams, reported the following results of the election: President—A. H. Smith, Vice-President—R. M. Bethke, Councilor—H. J. Almquist, Editorial Board—H. J. Deuel, Helen T. Parsons, V. P. Sydenstricker.

The Council recommended that the following be elected to membership: Georgian Adams, L. Atkin, R. A. Brown, V. H. Cheldelin, D. M. Greenberg, P. Handler, E. L. Hove, R. E. Johnson, A. R. Kemmerer, Helen Oldham, Aline Underhill Orten, J. J. Pfiffner, E. E. Snell, L. D. Wright.

This recommendation was approved and the above candidates were elected.

H. E. Carter announced the initiation of a new publication—“Biochemical Preparations”—for the purpose of publishing detailed, checked preparations of compounds of biochemical interest. He announced that the Editorial Board would be happy to have suggestions of suitable preparations or of preparations which the author would be willing to submit.

Dr. E. W. McHenry moved that the Council give consideration to the character of the annual meetings to the end of improving them in any way possible. This motion was seconded and approved. It was suggested that the Secretary circularize the membership soliciting suggestions on this point.

Dr. Rose announced that Dr. Ivvy, Dr. Carlson, and others had organized a group called “The National Society for Medical Research” whose objective is to educate the public as to the necessity for and methods of carrying on animal experimentation. He also pointed out that a similar group in New York called “The Friends of Medical Research” had been active for some time. The American Institute of Nutrition adopted the following resolution with regard to these organizations:

Be it resolved that the American Institute of Nutrition expresses enthusiastic approval of the purposes of the National Society for Medical Research and will recommend further action when the most effective means of assistance becomes evident and the American Institute of Nutrition also endorses most heartily the activities of the Friends of Medical Research.

The Secretary announced that the Council had refused a request by the Union of American Biological Societies that the Institute become a member of that Society.

The Institute gave a hearty vote of thanks to the Local Committee for their fine service in organizing and arranging the meeting. The Secretary was asked to send a letter of thanks to the local committee.

President Rose appointed the following Nominating Committee for 1946–47: Dr. I. McQuarrie, Chairman, Dr. Harold Goss, Dr. T. S. Hamilton, Dr. H. E. Longenecker, Dr. E. W. McHenry.

The meeting adjourned at 11:45 A. M.

Presentation of Awards Immediately preceding the business session the Mead Johnson Prize and the Borden Award were presented. Drs. Genevieve Stearns and P. C. Jeans as co-recipients of the Borden Award received medals and checks in recognition of the honor. Drs. I. C. Gunsalus and E. E. Snell received scrolls and checks as co-recipients of the Mead Johnson Prize.

AMERICAN PHYSIOLOGICAL SOCIETY

SYMPOSIUM ON PHYSIOLOGICAL CONTRIBUTIONS TO WAR PROBLEMS

H. C. BAZETT, CHAIRMAN

University of Pennsylvania, Philadelphia

In opening the meeting I want first to draw your attention to the main object of this symposium. You will hear a short resumé of some of the contributions of our members to the war effort. The subjects chosen have been selected, not because factors of particular physiological interest were uncovered, but rather because a real contribution was made to the health and efficiency of our forces. It is important that the Society should give thought to these past activities and that it should decide how far they should be continued in peacetime. The reports that you will hear will not be limited to accounts of work carried out under O. S. R. D. Our members were equally concerned in working for the Canadian N. R. C., and for the American or Canadian Forces. We, as a Society, are proud of their contributions without regard to the channels through which they worked.

In aggregate the contributions were important, though individually the advances achieved often seemed small. They consisted mainly in the application to practical problems of fundamental principles that were already well known to scientists, but unfortunately unknown to the general public or to the services. The efforts of many of our best physiologists were, therefore, expended doing chores. You will be familiar with the large group of first class physiologists who were occupied almost exclusively with administrative work, from Banting, Best & Bronk at the beginning of the alphabet to Richards and Weed near its end. Many of you are probably unaware of the lesser chores carried out faithfully by other members far too numerous to mention. These had the job of selling physiological ideas to the services. They spent their time teaching general principles, testing oxygen and other protective equipment, devising better test methods, or field modifications of test methods, and starting propaganda for the development of better equipment. The devoted services of these men was invaluable. It is unfortunate that time does not allow the additional inclusion of reports on more fundamental studies or on important analytical tools. Work of high merit was achieved in spite of the difficult conditions. These receive no direct attention here, since for the most part they came too late to have any great influence on the efficiency of the troops, though they added to our basic scientific capital. A few examples may be mentioned: the beautiful analysis of the factors contributing to "bends" by

Newton Harvey and of the mechanics of respiration by Wallace Fenn.

I would not have you conclude that the list of subjects, chosen for presentation exhausts even the war-time practical applications of physiology, far from it. Let me use a single illustration. Many of you have seen public movies of the "frog men", who did so much to help clear the beaches. Equipment was devised for these men which allowed them to travel over a mile under water and to stay below water for periods exceeding 3 hours. Work on this problem proceeded in England, and in enemy countries, as well as over here. The equipment ultimately used was, however, little dependent on team work or even on learning from our enemies. It resulted almost entirely from the work of one man, Christian Lambertsen, who at the start of the war was a medical student. He developed the equipment, trained the men, supervised their actual operations and in addition even persuaded the British to adopt American equipment. I hope that we may soon be able to count him among our members.

The speakers will review the work in general. They have been selected from the rank and file of the civilian workers, if you will pardon this mixed metaphor. Neither the main organizers of the Committee work nor the large group of service workers are represented, but this in no way implies any lack of appreciation of their excellent work.

The war-time research work selected for presentation is a tribute to magnificent team work. The machinery of coordination had to be improvised quickly and was often clumsy. The will to co-operate overcame the numerous difficulties. Work originating in Canada and Australia was developed to greater potentialities in the States, and American equipment in turn was adapted for use in England, Canada or Australia so that it coordinated with their already existing equipment. In all my contacts I found international scientific jealousies at a far lower level than the petty competitive rivalries that developed between the various services within each individual nation. The scientists can pride themselves in leading the world in demonstrating cooperation. Let us see to it that we continue to set such an example.

The rapidity of the progress attained depended on the pre-war existence of a large mass of basic information which could be put to immediate application. We may take great pride in the existence of this scientific capital. It is now our duty

to replenish it by fresh advances in basic science. It is less to our credit that this fund of information, capable of being applied practically, had not really been productive before the war. We must take care that such careless waste of intellectual capital does not occur in the future.

While I have little doubt that you will find the presentation interesting, I want you each to think beyond this and decide what contribution you yourself can make to speed scientific progress in the near future. Those of us who are relatively senior have a special responsibility towards the younger men. The productiveness of these men in the war has been remarkable. To some extent this depended on a financial status in war that was more assured than it is in peace. It is essential that we make determined efforts to obtain reasonable salaries for such men, so that they can continue to devote their whole energy to Science. Not only must they be able to work, they must also be able to live and multiply. If we fail to provide good conditions for the development of such stock, it will be a catastrophe for the country.

Again all of us, young and old, have other responsibilities. There appear to me to be 3 major ones. The first is to extend our basic knowledge, to reconstitute our scientific capital and to rise above doing mere chores. The second is to plan improved facilities for contact with medicine and industry, so as to ensure a more rapid practical application of new knowledge. This second implies seeing that the chores are done. Doing the chores may often not be our job but even so it would be better that we should do them, rather than that they should be left undone. Also the methods adopted for obtaining cooperation should be less clumsy than were those of the war period. The third is of supreme importance, we must work to obliterate national, racial, and individual jealousies in science at least, and if possible in broader fields. We must strive assiduously for the pooling of scientific knowledge and the removal of all such restrictions that seem to us unwarranted, so that scientific advances may serve all mankind.

HIGH ALTITUDE PROBLEMS IN AVIATION

A C IVY

Northwestern University, Chicago, Ill

We are gathered here to review in a brief way a small fraction of the physiological contributions to the solution of war problems. Although I have been assigned the topic of "High Altitude Problems in Aviation", I am more concerned regarding the future of research in aviation physiology than I am regarding the remarkable contributions already made by physiological and engineering science to flight at high altitude.

The Number One Problem in Aviation Physiology World War II has again proved that the possession and application of scientific knowledge is a matter of life or death. Physiological knowledge is no exception.

It was not an accident that physiology was able to provide the data required for the development of oxygen equipment for flight at high altitude and to indoctrinate tens of thousands of civilians regarding its use. It was not an accident that physiology could contribute to the nutritional and environmental welfare of our fighting forces. Physiology was able to make these and many other contributions because it had a stockpile of knowledge accumulated by patient research on apparently academic subjects, and because it had well developed specialized techniques and several hundred trained physiologists capable of applying successfully their training to new problems. This

was the greatest contribution of physiology to the successful conclusion of the War.

The physiological knowledge and personnel were available only because of the support given to academic research during peace. However, prior to the recent war, research in aviation and environmental physiology was at a low ebb because it was poorly supported. As a consequence, *time was lost* in translating physiological knowledge and techniques to field conditions and in the discovery and development of new knowledge of strategic importance.

Time as well as knowledge will be essential for success in the case another emergency rises. For these reasons I believe that the number one problem in aviation physiology is to find ways for maintaining research and development in this field.

The Solution of the Problem History reveals that one cannot be sanguine regarding the solution of this problem.

World War I found our Armed Forces largely unprepared in the field of Aviation Physiology. Early in 1918 an Air Service Medical Research Laboratory was established at Mineola, Long Island. Though the scientists at this laboratory made important contributions, the laboratory was abandoned in 1920. World War II again found our

Armed Forces largely unprepared in the field of Aviation Physiology. They would have been completely unprepared save for the contributions of Grow, Armstrong and Heim in the Army, Behnke and his colleagues in the Navy, and Boothby and his colleagues at the Mayo Clinic.

I have heard men say that this history will be repeated again, that it will not be long before we shall witness the collapse of the wonderfully well-equipped physiological laboratories in the Armed Services, that the salaries offered to scientists cannot compete with those offered by university and industrial laboratories, that existing administrative conditions in the Military Establishments are not as conducive to research as they should be, that the scientists required are not available because Selective Service has prevented the universities from training scientists during the War, that the scientists, who under the incentive of War have contributed so much to aviation, will return and are rapidly returning to their former research interests, that Congress will soon forget the need of the Armed Forces for scientists and scientific investigation in the field of Aviation Physiology, and that when military appropriations are reduced, research development, as in the past, will be the first to be radically cut.

These pessimistic predictions point the way to the solution of the problem.

There are current hopeful signs, not prevailing after World War I, which indicate that the problem may be solved. One of these signs is the proposed Division of National Defense of the National Science Foundation, which is being viewed favorably by Congress. This agency, if established, should promote coordinated research in aviation physiology and aircraft development. Either this agency, or other agencies in the Army and Navy should also provide for the continuance of intensive research in aviation physiology in a selected group of Service and Civilian institutions. This subsidization is necessary because the equipment required is expensive and specialized. My experience has convinced me that it is necessary to conduct research on aviation and environmental physiology in both military and civilian laboratories. And, it is to be hoped that when appropriations to the military services are reduced that research and development will not be starved out. It is better to have a small superlatively equipped and well-trained standing Army and Navy than it is to have large ones which are poorly equipped. Another favorable sign is that concern has been shown about the alarming rate of return of commissioned reserve and civilian scientists from the laboratories of the Armed Services to their pre-war posts and that the difficulty of recruitment of scientists for Service laboratories has aroused apprehension.

A view of the British approach to the problem is enlightening. The British Government has acted to render a career in scientific research in Governmental laboratories more attractive (1). Salaries have been substantially increased, the rapid promotion of young men of merit has been facilitated, scientists of ability who dislike administrative work may receive as much salary as administrators, and the attendance of scientific meetings has been encouraged. The Barlow report to the British Government contains some statements which are pertinent to the conditions which have in the past rendered scientific work in the Services unattractive. For example, "Young scientists, ambitious to obtain recognition for their work and to keep abreast of new developments, are discouraged from embarking upon a career which appears to remove them from contact with Universities, with learned societies and with the research side of industry." "We regard it as most important that wherever it is practicable (and it is obviously not always so) researchers, and in particular the younger men, should when personally suitable remain associated with the development of projects which they themselves have started." I should add here that in the U. S. Services, there is not only danger of being dissociated from a particular research project, but the greater danger of being dissociated from research in general in the name of that apparently immutable principle that all soldiers should and shall perform all types of duty. "We have gained the impression from various quarters that one of the factors that make scientific work in the Service Departments unattractive to prospective candidates is the control of civilian scientific staffs by officers of the Fighting Services." In this connection it should be pointed out that in the case of both civilian and military scientific staffs, the control and the rendering of scientific decisions is too frequently exercised by untrained and non-professional administrative officers to whom research and development constitute the most dispensable function of a military organization. Too frequently the administrator is unfamiliar with the experimental method and the scientific temperament, he does not know why a scientist is a scientist. In fairness it should be stated that notable exceptions to this criticism exist. "It is urged that the research worker should have within easy reach of his laboratory an adequately equipped workshop where he can get made quickly and under his own eye or with his own hands such rough and ready apparatus or alterations to existing apparatus as he requires for the immediate working out of his ideas." Thus we see that our British fellow scientists have taken firm positions on the problems that here confront us.

There are no sound reasons why a career in

research in the laboratories of the Services cannot be made as attractive as a career elsewhere. I do not mean to imply that outstanding researches have not been performed in the Service laboratories in peacetime or in the absence of the incentive of war and under existing conditions of organization. But, these could be multiplied by improving the conditions.

I hope that another Great War will not occur. But, if it does it appears certain that our success will depend more than ever on the knowledge and equipment developed during the intervening period of peace. For this reason the establishments for research and development in the Army and Navy should be well supported and coordinated with subsidized research in civilian laboratories. If a Great War does not occur, knowledge will have been gained which will undoubtedly be applicable to peacetime pursuits and the general welfare of our people.

Scientific Contributions to and Problems of High Altitude Flight. During the recent War our knowledge regarding many topics pertaining to aviation physiology was increased. However, many observations and reports are still "closed", and I am confined to those which have been published, the "open" observations I have made, and a theoretical analysis of certain problems. The topics which I propose to summarize briefly and in a general way are oxygen requirements, pressure breathing, decompression sickness and explosive decompression.

Oxygen requirements. In supplying oxygen several major questions arise. The first of these is:

At what altitude should oxygen administration start? Prior to the recent War it had been found that a significant number of persons manifest deterioration of certain visual functions at 10,000 or 12,000 ft (2-4), an occasional individual will show detectable deterioration at 8,000 feet. For example, relatively mild anoxia apparently slows the rate of dark adaptation (5). For these reasons, it has been considered advisable to start oxygen supplementation at 5,000 ft for night and 10,000 ft for day flight.

For practical reasons it has been important to know how long "useful consciousness" will persist after the oxygen supply has been discontinued at high altitudes. This has been determined by removing the oxygen supply of subjects at different altitudes and observing how long the subjects continued to write a simple sentence. It was found that an altitude of 26,000 ft is critical in that none of 49 subjects at this altitude were able to continue writing longer than 15 minutes (7). At 25,000 ft, 2 of 52 subjects were able to continue writing longer than 15 minutes. At 28,000, 30,000, 32,000, 34,000, 36,000 ft the mean period of useful consciousness was re-

spectively 30, 24, 18, 14, and 12 minutes (7) (table I). The ability to write persisted at arterial oxygen saturations greater than 66 per cent (range 56 to 66, average, 62 per cent) (8). Providing for a small margin of safety, seventy-five per cent saturation is the lower safe limit for voluntarily directed movement (8).

Another important question arose when the device for regulating the oxygen supply was being developed. This was: *What is the optimum mixture of 100 per cent oxygen and air at levels up to the altitude at which the aviator should breathe 100 per cent oxygen?* From the viewpoint of decompression sickness, 100 per cent oxygen should be breathed from the ground up. From the viewpoint of the conservation of the oxygen store in the plane, oxygen should be mixed with air until an altitude is reached at which 100 per cent oxygen is

TABLE I

Time of exposure at altitude required to produce critical symptoms of anoxia (7)

ALTITUDE	PERIOD OF USEFUL CONSCIOUSNESS*	NO. OF SUBJECTS
(ft)	minutes	
20 000	40% of group still writing at 15 min	
25 000	4 5	52*
26 000	3 7	49
27 000	3 4	55
28 000	3 0	52
30 000	2 4	49
30 000	2 1	123 (8)
32 000	1 8	49
34 000	1 4	51
35 000	1 2	73 (8)
36,000	1 2	42

* Two men still writing at 15 min. Rate of ascent to altitude was 2 000 ft./min. with O₂ by demand regulator from 10 000 ft up. (7) and (8) refer to the authors.

required to maintain 95 per cent saturation of the arterial blood.

This question is readily answered by using the alveolar equation. The results of the calculations are shown in table II for the maintenance of an alveolar pO₂ equivalent to sea level and to an altitude of 5,000 feet. There are no published data showing that these calculations do not apply in practice.

The data in table II and table III show that breathing pure oxygen at 33,700 ft at ambient pressure reproduces an alveolar pO₂ equivalent to sea level. Above this level pure oxygen will not yield a normal alveolar pO₂. At an altitude of 39,700 ft, the breathing of pure oxygen at ambient pressure yields an alveolar pO₂ equivalent to 10,000 ft breathing air. Breathing pure O₂ at 46,800 ft is equivalent to breathing air at 25,000 feet.

Thus, if an alveolar pO_2 equivalent to 10,000 ft breathing air is to be maintained above an altitude of 39,700 ft the alveolar pO_2 must be increased above that obtained by breathing pure oxygen. Above 39,700 ft the alveolar pO_2 can only be increased by hyperventilating with pure oxygen or by breathing oxygen under pressure. The latter is obviously preferable up to that

TABLE II

Showing the Oxygen content of the inspired air required to maintain an pO_2 equivalent to sea level and an altitude of 5,000 ft

ALTITUDE	SEA LEVEL EQUIVALENT	5 000 FT EQUIVALENT
ft	% O_2	% O_2
0	21.0	17.2
5,000	25.5	21.0
10,000	31.3	25.7
15,000	38.8	31.9
20,000	48.8	40.1
25,000	62.4	51.3
30,000	81.2	66.7
35,000	108.7	89.0

$$\text{Formula for sea level \% } O_2 = \frac{151}{B-40} \times 100$$

$$\text{Formula for 5 000 ft \% } O_2 = \frac{101}{B-42} \times 100$$

At 33,700 ft 100% O_2 is the sea level equivalent

TABLE III

Calculated from the alveolar equation

BREATHING AIR		R Q	UNSTEADY STATE			BREATHING 100%	
Alt	Bar Pr		Alveolar composition			O Bar	Pr Alt
			pO	pCO ₂	pH ₂ O		
0	760	0.85	104.1	40.0	47	191.1	33,600
2,500	694	0.85	90.3	40	47	177.3	35,200
5,000	632	0.85	77.3	40	47	164.3	36,800
7,500	575	0.86	66.3	39.5	47	152.8	38,300
10,000	523	0.88	57.5	38.5	47	143.0	39,700
12,500	474	0.92	50.0	37.0	47	134.0	41,000
15,000	429	0.97	44.4	35	47	126.4	42,300
17,500	387	1.05	40.0	32.5	47	119.5	43,400
20,000	349	1.13	36.2	30.0	47	113.2	44,600
22,500	314	1.24	32.7	27.5	47	107.2	45,700
25,000	282	1.36	29.6	25.0	47	101.6	46,800

Note that roughly 1000 ft above 34,000 ft breathing pure O_2 is equivalent to 2000 ft above sea level. Above 33,700 ft, 100% O_2 will not give a normal alveolar pO_2 .

amount of pressure which harmfully impairs venous return

Pressure breathing The breathing of oxygen under pressure greater than the ambient pressure is called pressure breathing. This procedure was used therapeutically before the War (9-11) for the treatment of various pulmonary conditions, such as pulmonary edema, asthma, pneumonia, and bronchitis.

Pressure breathing raises alveolar pO_2 theoretically only by increasing total pressure. Thus, the gain in altitude is equal to the decrease in pressure altitude in the chest. The altitude gains, calculated for different pressures, are shown in table IV. The theoretical ceiling under the condition of breathing pure oxygen under 18.8 mm Hg pressure and hyperventilation to decrease the alveolar pCO_2 may be calculated as follows: $(pH_2O) 15$ (Christie and Loomis) + $(pCO_2) 15$ (requires marked tolerance to hyperventilation) + $(pO_2) 38$ (equivalent to 18,000 ft) equals 98 mm Hg, 98 mm Hg minus 18.8 mm Hg pressure above ambient equals 79.2 mm Hg, which is equivalent to 52,000 feet.

Theoretically there are two possible ways to increase the mean pressure in the lungs. One is to apply the pressure continuously throughout the

TABLE IV

Theoretical gain in ceiling by breathing Pure O_2 above ambient pressure

PRESSURE USED		ANOXIA EQUIVALENT TO 10,000 FT		ANOXIA EQUIVALENT TO 15,000 FT	
Inches H_2O	Mm Hg	Unsteady State Max Altitude	Gain in Altitude	Altitude	Gain in Altitude
			ft	ft	ft
0	0	39,700	0	42,300	0
4	7.5	40,900	1,200	43,500	1,200
6	11.3	41,500	1,800	44,200	1,900
8	15.0	42,200	2,500	44,900	2,600
10*	18.8*	42,800*	3,100	45,600	3,300
12	22.5	43,500	3,800	46,400	4,100
14	26.3	44,200	4,500	47,100	4,800
16	30.0	44,900	5,200	47,900	5,600

* Example, using table III for 10,000 ft $(pH_2O) 47 + (pCO_2) 38.5 + (pO_2) 57.5 = 143.0$ mm Hg - 18.8 mm Hg (Pressure Breathing) = 124.2 mm barometric pressure, or 42,800 ft

respiratory cycle. The other is to apply the pressure intermittently, having the highest pressure occur either during the inspiratory portion of the cycle or the expiratory portion of the cycle, or the inspiratory portion of the cycle may rise rapidly to a peak and the expiratory portion fall over a prolonged period. The theoretical difficulty with the intermittent method is the danger of excessive hyperventilation. The abnormality inherent to the use of both methods is interference with venous return, this should not occur to a harmful extent with mean pressures of less than 12 to 15 mm Hg.

Doctor Gagge, who pioneered the application of pressure breathing to the gaining of altitude, has used the method of continuous pressure, which was adopted by the A. A. F. Gagge, Allen and Marbarger (12) have reported their experimental results. They have found that breathing against

a continuous pressure of 15 mm Hg (8 in H₂O) is tolerated "by nearly all normal and trained individuals" Breathing against such a pressure at 45,000 ft has resulted in blood oxygen saturations equivalent to those found in subjects breathing air at 15,000 feet This approximates the theoretical calculations shown in table IV

Pressure breathing is obviously physiologically abnormal and subject to limitations But, it should be pointed out that the resistance to expiration is felt much less at altitudes above 35,000 ft than it is at ground The physiological data collected on pressure breathing during the War in various laboratories, here and abroad, will be found to be most interesting when published

Decompression sickness A tremendous amount of data has been collected on the subject of decompression sickness The American data will be presented in the form of a book under the editorship of Doctor Fulton I am informed that the data from the British and Canadian laboratories are also being prepared for publication The data may be grouped primarily into four categories, namely, (a) the mechanism of bubble formation and the cause of decompression sickness, (b) the symptoms, (c) the factors which influence susceptibility, and (d) the problem of preselection for susceptibility to "bends" and "chokes"

The mechanism of bubble formation and the cause of the symptoms of decompression sickness has been studied particularly by Newton Harvey (13), Whitaker and Blinks (14), and Gersh (15) and their colleagues Their observations confirm the previous view, which has been summarized by Harvey (13) as follows "Some details remain to be filled in but on the whole the etiology of decompression sickness can best be expressed by one word—bubbles" The bubbles are located primarily on the venous side of the circulation, and in the tissues Ferris and his colleagues found early that the arterial blood is rapidly cleared of nitrogen following the inhalation of oxygen At altitude, exercise and muscular tension as first emphasized by Ferris and his colleagues (18) markedly facilitate the formation of bubbles Clearing the body of nitrogen before ascent prevents their formation (13) It is not surprising then that denitrogenation or the removal of most of the one liter of gaseous nitrogen in the human body, a procedure used by Behnke in 1937 (16), is the most practical method for preventing decompression sickness

Harvey, McElroy and their colleagues (20) have emphasized the importance of carbon dioxide in the initial growth of bubbles in the cat, pointing out that an extreme reduction in carbon dioxide concentration would increase the degree of mechanical tension necessary for bubble formation This appears to hold also for man, since

hyperventilation to the point of tingling and carpopedal spasm in human subjects definitely decreases the severity of "bends" at 40,000 ft (21) (See Table V)

The symptoms which result on exposure to high altitude are many and varied However, in the altitude chamber the chief causes of descent in order of their frequency are "bends" (73 per cent), "chokes" (17 per cent) and abdominal gas pains (13.6 per cent), as determined by a study of 852 cases of forced descent (17)

The symptoms are not uniform in severity At least three grades of the severity of "bends" occur at altitude, that which disappears at altitude, that which persists but does not cause descent, and that which causes descent from incapacitation "Chokes" are less likely to disappear at altitude Descent is the specific treatment for "bends" and "chokes", though disturbing symptoms may

TABLE V

Showing effect of hyperventilation on the descent rate due to bends and chokes

40,000 ft for 1 hr without exercise, 50 subjects in each group

	A		B		C		B + C	
	Control Group		Vol Hypervent		Mechan Hypervent			
	No	%	No	%	No	%	No	%
Total Symptoms	28	56	22	44	19	38	41	41
Total tolerable bends and chokes	18	36	18	36	16	32	34	34
Descents from bends and chokes	10	20	4	8*	3	6†	7	7‡

* Chi Square = 2.99 (p = 0.08)

† Chi Square = 4.33 (p = 0.037)

‡ Chi Square = 8.9 (p = 0.0023)

occasionally persist, recur, or even occur no descent (17)

The exact site of the stimulus causing the pain of "bends" is uncertain, even though numerous x-ray studies have been made According to our (24) observations, similar amounts of gas may be present about the knee or wrist joints with pain in one knee or wrist and not in the other Or, pain may occasionally be present in a joint without there being x-ray evidence of gas However, statistically speaking, gas in the fat or fascia about the joints or between muscles is associated with pain Some individuals have "critical foci", or areas in which pain in association with x-ray visible gas always occurs The pain is frequently very severe, and moderate doses of analgesics, including 15 mg of morphine sulfate, have little effect on the incidence of descents due to bends

"Chokes" is apparently associated with bubbles

in the arterioles of the pulmonary artery, i.e., pulmonary aerocombolism. In man, enlargement of the right heart has been reported to occur in "chokes" (25), and we (21) have one roentgenogram showing enlargement of the maximum transverse diameter of the heart in a subject with "chokes".

1 number of factors predispose to the occurrence of bends. The cause of the rather marked variation in the susceptibility of individuals of the same age, sex and obesity is unknown.

In a youthful population homogeneous as regards age and sex, altitude and exercise (18, 18a) are the most important factors. The descent rates of two-hour flights at 33,000, 35,000 and 38,000 ft when plotted against the altitude yields a linear relationship (17). When a mild exercise is added (5 deep squats and 5 push ups from side of altitude chamber), the descent rates at the various altitudes including 30,000, 27,000 and 23,000 ft increase in a linear manner, and the altitude threshold is decreased to an altitude of 23,000 ft. This threshold approximates Haldane's (19) estimate from his study of divers, that bends should occur at an altitude of 21,000 ft (a change from 2.25 to 1 atmosphere, or, $1 \text{ to } 0.44 = 21,000 \text{ ft}$), since his subjects ascending from high pressure to sea-level were exercising.

It has been established that factors other than altitude and exercise influence the incidence of "bends" and "chokes". For example, observations made in aero-medical units show that the incidence of bends is related to the *time of day*. The incidence is greater in the morning than in the afternoon and evening (22, 23). The explanation of this is not clear, though a circulatory factor has been suggested. The incidence of bends varies month by month for some unknown reason and does not appear to be clearly related to the Season (23). The composition of the diet is not a significant factor, though a very high protein diet predisposes to bends (24). As age, weight and linear density increase, the incidence of total and unbearable bends increase (23). Race and nationality appear to be factors, since the rate of descents observed by one aero-medical unit of the Army was greater in American whites than negroes and less in French than negroes (23). The incidence of bends and chokes also varies with the amount of denitrogenation which occurs during ascent to altitude. Fifteen minutes of breathing of pure oxygen before reaching an altitude of 23,000 ft is definitely effective in reducing the descent rate in the absence of exercise (17).

The preselection of personnel for susceptibility to bends and chokes is a difficult problem. Early in the War it was assumed that one "pass or fail" exposure to altitude would be adequate. This was soon found not to be valid because it was based on

the false assumption that an individual was either completely resistant or completely susceptible. Since then, a large amount of work has been done by Canadian and American laboratories to find a relatively accurate and practical method of preselection.

Since individuals vary in regard to susceptibility, the matter of preselection is a statistical or actuarial problem. It can be solved either by exposing an individual repeatedly so as to determine his mean susceptibility or by determining the mean susceptibility of a large group to a standard flight. Predictions based on the results of a standard flight would be more reliable if the standard flight provided a mean susceptibility of 50 per cent for a large homogenous group. The results of the standard flight could then be used to

TABLE VI

Showing the selection obtained by exposing a group of 100 subjects five times

Seated at 38,000 ft for 3 hrs., rate of ascent 4000 ft/min

PREVIOUS FLIGHTS DESCENTS NO	TOTAL		DESCENTS THIS FLIGHT	
	No	%	No	Rate %
First flight				
Total	100	100	30	30
Fifth flight				
0	40	40.0	4	10.0
1	29	29.0	4	13.8
2	15	15.0	6	40.0
3	11	11.0	7	63.6
4	5	5.0	4	80.0
Total	100	100.0	25	25.0

On the fifth flight the descent rate for the group was 25%, whereas the descent rate for the 40 which had passed 4 flights was 10%.

divide a population into groups and to test the reliability of other selection procedures which might be more practical. Unfortunately a standard flight with a mean incidence of 50 per cent was not defined and established during the War, though observations were made using many different flight conditions.

An example of how the exposure of the same group to the same flight conditions five times selects the most resistant and the most susceptible groups will be given. A group of 100 subjects were exposed seated to 38,000 ft for 3 hours, having ascended at a rate of 4,000 ft per minute. The rate of descents from all causes was 30 per cent during the first flight. During the fifth flight, only 4 or 10 per cent of the 40 that had passed four flights had to descend,

whereas 24 or 24 per cent of the entire group of 100 subjects had to descend. Thus, by selecting from a group of 100 subjects a group of 40 subjects who had not descended during four exposures, the rate of descents had been reduced from 25 per cent for the entire group of 100 to 10 per cent for the selected group of 40 (table VI). Unfortunately a reliable substitute for the procedure just cited has not been found.

It would appear that a combination of preoxygenation and elimination of the most susceptible by preselection is the most certain and effective method to prevent bends at altitude when physical work is required.

Comment When one considers the numerous problems of flight at high altitude, such as mask leaks, failure of oxygen supply, the limitations of pressure breathing, the occurrence of "bends", "chokes", and gas pains, the pressurized cabin is the obvious solution. However, when the cabin loses pressure from enemy action or an accident at an altitude of 42,000 ft or above, the problems listed arise as an emergency. In addition, the use of the pressurized cabin gives rise to another problem, namely, "explosive decompression".

Explosive decompression The distinction between a rapid and an "explosive" decompression has not been clearly defined. When "explosive decompression" was first considered by Armstrong (26), he assumed "that within a reasonable period of time airplanes would be developed which would climb at a rate of approximately 5,000 ft per minute." He then defined "explosive decompression" as "all rates of decompression greater than those which would occur during such an actual rate of ascent." At present, any rate of decompression greater than 5,000 ft per minute from a stated altitude is referred to as "explosive decompression." In time, the expression will probably be defined on the basis of pounds per square inch per second, or more precisely as a fraction of the function of the factors concerned in producing pulmonary damage.

Behnke (27) and Polak and Adams (28) in 1931 reported two fatalities from rapid decompression during a study of the use of the "Momsen lung" which was being used for escape from submarines. Hemorrhages in the lungs were found. Behnke explained the accidents as due to a too rapid rate of decompression which prevented equilization of the intrapulmonic pressure with the external pressure. On the contrary, Armstrong (26) as the result of experiments on animals and human subjects expressed the view that "the effects of 'explosive decompressions' are determined principally, not by the amount of pressure differential, or the rate of pressure change, but by the ultimate altitude attained."

In studying the various factors concerned in the

cause of damage due to rapid decompression, species differences have been found as regards susceptibility, the type of damage of the lung, and the distribution of the damage between the lung, gastrointestinal tract, and ear. Our (30) results on rabbits, swine, dogs and monkeys are shown in table VII.

The results of a number of studies on animals reported in the literature show that the rate of increase in intrapulmonic pressure is important in rupturing the pulmonary epithelium and capillaries (29, 28). For example, an intratracheal pressure of 80 to 100 mm Hg, when sustained for 10 seconds, will cause air to pass into the blood in the pulmonary veins (dog). However, a sudden increase in intrapulmonary pressure of 80 mm Hg

TABLE VII

Species difference in susceptibility to rapid decompression from ground to 40,000 ft, rate, 1,500,000 ft per sec or 484 lbs /sq in /sec

SPECIES	NO	% EAR DAMAGE	% LUNG DAMAGE	% IN JURED	DEATHS
Rabbits	12	33	92	100	0
Swine	19	79	84	100	2
Dogs	31	61	39	77	0
Monkeys	10	40	20	40	0

There were no injuries of the eye

TABLE VIII

Relation of rate of decompression to lung injury, altitude constant, ground to 40,000 ft, dogs

RATE OF DECOMPOSITION	NO	% LUNG DAMAGE
1 550 000 ft per sec	39	41
440 000 ft per sec	10	20
225 000 ft per sec	9	10

(1.5 lbs per sq in) for 1 second in dogs does not cause injury (10 dogs), whereas, 97 mm Hg (2 lbs per sq in) for 1 second causes injury in 70 per cent of dogs (3 out of 10) and death from pneumothorax in 40 per cent (30). A sustained intratracheal pressure of 24 mm Hg (32.6 cm H₂O) produced by a continuous stream of air introduced through a tracheal catheter causes interstitial and mediastinal emphysema in dogs (31).

Using dogs, we (30) have obtained evidence that the rate of decompression, as regards lung damage, is more important than the pressure difference through which the animals are decompressed. The trends are indicated in tables VIII and IX, though more animals should be used to show that the differences are not due to a sampling error.

All of the lesions observed by us (30) in rabbits, swine, dogs and monkeys, were confined to the

lungs and ears Ataxia was present in some animals for a brief period after descent We did not observe paralysis as has been reported by others Neither did we find gastrointestinal rupture and hemorrhage, which has been observed by some investigators in rabbits, guinea pigs, and rats (32)

At rates of decompression up to 1,500,000 ft per second, or 464 lbs per sq in per second, we (30) observed in dogs only transient changes in blood pressure amounting to 20 or 30 mm Hg, the electrocardiograms were essentially normal White horn, Edelmann and Hitchcock (33) noted a transient drop in blood pressure at rates above 20 pounds per sq in per second

During the War many experiments have been performed on many *volunteer human subjects* chiefly by Smith (32), Sweeney and Joffe (35, 37), Hitchcock, Edelmann and Whitehorn (31), Gressley (32), and Doering and Hornberger (32) More than 1000 experiments have been done on over 250 subjects The subjects were exposed to differential

TABLE IX

Relation of altitude to lung injury, rate constant, 1,500,000 ft/sec, dogs

DECOMPRESSION	NO	% LUNG DAMAGE
Ground to 40,000 ft } Ground to 37,500 ft }	39	41
35,000 ft	9	56
30,000 ft	4	75
25,000 ft	5	60
20,000 ft	5	40
15,000 ft	16	73

pressures varying from 10 to 84 lbs per sq in at decompression rates of from 16 to 200 lbs per sq in per second Complications occurred in only 5 cases Two had mild transient pneumomediastinum, two, temporary "decompression apoplexy", and one, transient substernal pain and dyspnea on exercise a few hours after exposure, however, in no case was there any permanent effect All these cases with complications followed relatively "slow" decompression Sweeney and Joffe (37) performed 150 experiments in which the subjects were decompressed from 10,000 ft to 35,000 ft in 0.075 sec (Δp , 6.55 lbs per sq in), or at a rate of 87 lbs per sq in per second, or 330,666 ft per second All subjects had no difficulty in adjusting their oxygen equipment In decompressions up to 53,000 and 56,000 ft, observed by German investigators, an immediate and complete loss of sensation and inability to think and work was reported to occur

Gagge and Sweeney (36) have recently published an equation which is designed to define for practical purposes the safe limits of explosive decompression They concluded from observations on man that two physical factors are the most significant in determining the safe limits one is the relative expansion of internal gasses (RGE), and the other is the time of the decompression As the time of decompression increases, the expanding gasses have time to escape from the lungs and thus the maximum tolerable relative expansion of gasses would increase

The physical and mathematical analysis of the problem will not be considered here Such an analysis would indicate that several factors are theoretically concerned (a) The magnitude of the differential pressure developed across the lung wall, which depends on the relative rates of decompression of the cabin and lungs (b) The relative expansion of the internal gasses, which will determine the effectiveness of any given pressure differential in stretching the pulmonary walls to the fracture point (c) The rate at which the peak differential pressure is applied The elongation of elastic tissue requires a finite time A force applied very rapidly might not give the tissues sufficient time to overcome their inertia, and hence the force would be more damaging than one which was gradually applied (d) Vapor pressure, since the gasses in the lung are not dry, adds to the effectiveness of a given pressure differential at high altitudes (e) The stress strain properties of lung tissue We probably need more information on this point in order to treat the problem more precisely

The observations made on "explosive decompression" are exceedingly important It is obviously important to know that young adults may be decompressed from 8,000 to 42,000 ft, or from 27,500 to 45,000 ft, under conditions simulating those which may practically occur, and not be harmed The determination of the "safe limits" of explosive decompression are directly applicable to a new problem which has arisen as a result of the development in the field of jet-engine mechanics

A new problem It now appears certain that jet-engine mechanics will propel aircraft to altitudes and at rates expressed in miles rather than in feet per minute Undoubtedly pioneers will be found to fly such craft This raises the problem of escape and the development of auxiliary safety devices And, the problem of "explosive decompression" to a pressure altitude of 50,000 ft becomes only a part of the larger problem of "emergency survival in a vacuum"

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EFFECTS OF ACCELERATION IN RELATION TO AVIATION

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Force as a factor in man's environment Although this report is entitled, in part, "Effects of acceleration," actually the discussion is chiefly concerned with the effects of force on man. The human body is continually acted upon by the earth's force of gravity and is well adapted to existence in an environment with a force of this magnitude. However, the forces which are brought to bear on man by acceleration in high-speed, maneuverable aircraft can be many times greater. Man's susceptibility to changes in his force environment frequently makes him the limiting factor in the performance of his aircraft and in certain flight emergencies may lead to his injury or destruction.

Travel at high velocity has no effect on an aviator enclosed in his aircraft as long as the speed is uniform and the path of flight is in a straight line. However, the flyer becomes immediately aware of any considerable change in either the speed or direction of motion.

If the plane increases or decreases its speed, the pilot is pressed backward into his seat or forward into his safety harness by a force which is proportional to the rate at which his speed is changed. The force in these instances results from linear acceleration or linear deceleration. If the plane increased its speed at a rate of 32.2 feet per second per second, the pilot would be pressed against the back of his seat with a force equal to that of gravity. Since the force of gravity is so universally appreciated, and can be so readily determined, it is commonly used as a convenient unit of force known as a "g unit." The amount of force, expressed in g units, resulting from linear acceleration or deceleration can be calculated from the following equation:

$$g = \frac{v_1^2 - v_0^2}{64.4 s}$$

v_0 = original velocity in feet per second

v_1 = final velocity in feet per second
 s = distance in which the change in speed takes place
 g = force in g units

If the plane, traveling at a constant speed, flies in a curved path, the aviator is pressed downward into his seat or upward into his safety harness by a force, the magnitude of which may also be expressed in g units. The force in this instance results from centripetal acceleration and is commonly called centrifugal force. It can be calculated from the velocity of the plane and the radius of turn, according to the following equation:

$$g = \frac{v^2}{32.2 r}$$

v = velocity in feet per second
 r = radius of turn in feet

An additional type of acceleration, angular acceleration, occurs when both the speed and the direction of travel are changed simultaneously. Effects which are common to this type of acceleration—for example, disturbances of equilibrium and motion sickness—will not be discussed in this paper.

The effect of acceleration on a body is apparent as weight. The force of gravity gives man the weight to which he is accustomed. If by acceleration man's force environment were suddenly increased to 2 g, his body weight would be doubled, at 3 g it would be tripled, and so on. Each of his body tissues and fluids would become correspondingly heavier and would remain so as long as acceleration continued.

The effects of the force on man depend, however, not only on its magnitude but also on its rate of application, duration and direction. Accelerations of moderate magnitude (2 to 10 g) produce dramatic but reversible physiologic effects in man which become fully developed only when the force acts for several seconds. These effects are most pronounced when the direction of the force is through the long axis of the body in either the head to seat direction (positive acceleration) or the seat to head direction (negative acceleration). They are much less when the force acts across the long axis of the body (transverse acceleration). On the other hand, accelerations of great magnitude (more than 20 g) acting in any direction may produce structural damage to bones and tissues even though they occur for only fractions of a second. The effects are pathologic and may be lethal. In general, regardless of magnitude and duration, the effects of force are more severe the more rapid its onset.

Force, therefore, although not usually thought of in this sense, is a most important component of man's environment. Indeed, a change in man's force environment can produce effects as striking

as those produced by changes in temperature, pressure or oxygen tension.

Some of the circumstances in which man experiences acceleration in aviation (table 1). Linear acceleration occurs during catapult take offs, rocket or rocket assisted take offs, forced ejection of pilots from high speed aircraft and in the pick-up of human beings from the ground by planes in flight.

Because the linear acceleration ordinarily encountered in catapult and rocket assisted take-offs is small (usually less than 4.5 g) (1), of short duration and transverse in direction, it produces little effect and therefore has not constituted a serious problem. It is possible, however, that acceleration of this type may become a problem in rocket take offs in the future. For example, calculations based on the speeds which develop during the take-offs of the German V-1 robot bomb show that an average force of about 20 g must be developed for a period of about 0.5 seconds. A force of

TABLE 1

Aeronautical maneuvers involving accelerations which may produce physiologic or pathologic changes

-
- | | |
|-----|---------------------------------------|
| I | Linear acceleration |
| A | Catapult take-offs |
| B | Rocket or rocket assisted take-offs |
| C | Ejection from aircraft |
| D | Human pick up |
| II | Deceleration |
| A | Crashes, crash landings and ditchings |
| B | Escape from high speed aircraft |
| C | Shock of parachute opening |
| D | Shock of parachute landing |
| III | Centripetal acceleration |
| A | Escape from spinning aircraft |
| B | Flight in a curved path |
-

this magnitude would certainly be a hazard if human beings were ever to travel in such missiles.

In certain combat or rescue operations, it is of value to be able to pick up a human being from the ground by means of an airplane passing in flight. In this maneuver, the subject must be accelerated from 0 velocity on the ground to the speed of the pick-up aircraft. The United States Army Air Forces Aero Medical Laboratory at Wright Field attacked this problem during the war and the studies there led to the successful pick-up of man from the ground at aircraft speeds of 130 miles per hour (2). To accomplish this, mechanisms were devised whereby the pick-up was accomplished without the development of forces exceeding 7.5 g for periods longer than 2 seconds. Man can withstand such forces for this short period without serious consequence.

Deceleration constitutes a problem in airplane crashes, crash landings, ditchings, during escape

from high speed aircraft and during the opening of parachutes. The forces which occur in crash landings of aircraft may be extremely high and variable. For example if a plane traveling at 200 miles per hour were stopped in a distance of 6 feet, the plane would be subject to an average force of 220 g, acting for 0.04 second. Relatively little is known of the ability of human beings to withstand such forces, although interesting studies in this field are now in progress (3). The large number of fatalities in airplane crashes, and the thousands of people killed each year in automobile accidents are ample evidence of the importance of research into injuries produced by deceleration.

In the early part of the war, reports were received of injuries due to the forces produced by parachute openings at high altitude. The Aero Medical Laboratory at Wright Field carried out a most creditable investigation of this problem and found that parachute opening shock forces increase with altitude so that, at 40,000 feet, shock forces of 40 g may frequently be encountered (4). Forces of this magnitude are sufficient to cause bodily injury. Solution of this problem has involved construction of parachutes with opening characteristics which decrease the force and the development of procedures which allow man to fall safely to lower altitudes before the parachute opens (5).

Escape from aircraft traveling at very high speeds may be difficult or impossible because of the force of the windblast on the flyer as he leaves his airplane. At 600 miles per hour, the impact pressure of the slip stream is 921 pounds per square foot, which to the escaping airman is equivalent to a decelerative force of 30 g. The difficulty of escape from aircraft under these conditions has led to the development in Germany, Great Britain and this country of two pieces of equipment: first, ejection seats designed to explode the flyer out of the plane and, second, automatic devices which delay release of the parachute until the airman has slowed to his terminal velocity.

Centripetal acceleration, the last of the three types of acceleration which may produce traumatic or physiologic effects in man, is usually encountered in aircraft during spins or rolls and during turns and pullouts from dives.

In large aircraft, spins usually occur as a result of structural damage to the plane. It has been found that during spins forces of such magnitude may develop that escape of pilots and crew may be difficult or impossible, all occupants of the aircraft being immobilized by their increased weight which in turn is due to the forces generated by the spin (6). Studies have been carried out which emphasize the need for an explosive or other mechanism whereby the occupants of spinning planes can be expelled from their aircraft (7).

Centripetal acceleration arising during normal flight in a curved path is the most commonly experienced acceleration in aircraft. As a result of this acceleration occupants of conventional aircraft may be exposed to centrifugal force in either the positive (head to foot) or negative (foot to head) direction. With present aircraft, the forces developed may vary from a negative $\frac{1}{2}$ g to a positive 12 g and may be from less than a second to several minutes in duration. When such forces are sustained for more than 3 to 5 seconds, they may produce startling physiologic effects. The imposition of these effects on the pilot is often the limiting factor in the performance of the aircraft and in the offensive and defensive combat tactics to which the pilot can apply his aircraft.

The pilot experiences negative acceleration when he performs maneuvers with his plane in the inverted position, such as inverted turns and outside loops. His tolerance to centrifugal force acting in this direction (foot to head) is low. At 3 g he may experience pronounced discomfort in the head, reddening of vision ("redout") and, sometimes, persistent headache. Tactics involving the development of force in the negative direction have not been generally used and, as a result, the physiologic problems involved have not received extensive investigation, although important observations have been made by workers at the RCAF centrifuge Toronto, Canada.

Positive acceleration occurs during normal flight in banked turns and during pullouts from dives. When exposed to accelerations of 5 g or more acting in this direction (head to foot), most pilots suffer loss of vision (blackout) or unconsciousness (8). Since positive acceleration is unavoidable during tactical maneuvers in modern fighter aircraft it has been of great practical importance and has demanded continuous study by physiologists during the war. The problems which confronted the physiologist can be resolved into two questions: first, what are the medical and physiologic consequences to man of exposure to positive acceleration, and second, how can these effects be prevented? The remainder of this presentation will be devoted to studies on man which were designed to answer these questions. Few references will be made to work published in the open literature prior to 1943, since this has been adequately reviewed and discussed in the general articles and handbooks published by Ruff and Strughold (1) 1939, von Diringshofen (9) 1939, Grow and Armstrong (10) 1941 and Ham (11) 1943.

The human centrifuge. Early studies of the effects of centrifugal force on man were carried out in aircraft but in order to make observations under accurately controlled conditions it was necessary to reproduce the centrifugal force of flight in the laboratory. This required the con-

struction of human centrifuges of the type shown in figure 1. This is the most recently constructed human centrifuge in the United States and is located at the University of Southern California in Los Angeles. The subject sits at the periphery of the centrifuge, in a cab, facing in the direction of rotation. The cab swings outward during rotation of the centrifuge, so that the resultant force is in the direction from head to seat of the subject. The observer sits near the center of the centrifuge.

Modern centrifuges such as this can simulate the patterns of centrifugal force which occur in aircraft. Earlier human centrifuges did not, and many of the data obtained from them were not applicable to the pilot in his aircraft. While important pioneering efforts were carried out in Germany (12), Wright Field (13) and Australia (14), the first modern centrifuge which satisfactorily

stages of the war indicates the importance which was placed on the problem of centripetal acceleration by our own military leaders and by the German high command.

The effects of centrifugal force on man. The effects of centrifugal force on man are the result of the increased weight of the tissues of the body which the force produces. Since blood is the most mobile tissue in the body, the cardiovascular system is extremely susceptible to changes in man's force environment.

The effects of force on the hydrostatic pressure differences in man's vascular system are shown diagrammatically in figure 4. The ordinates on the left show hydrostatic pressure in millimeters of mercury and, on the right, arterial pressure also in millimeters of mercury. The first figure shows the average position of the pilot in an American

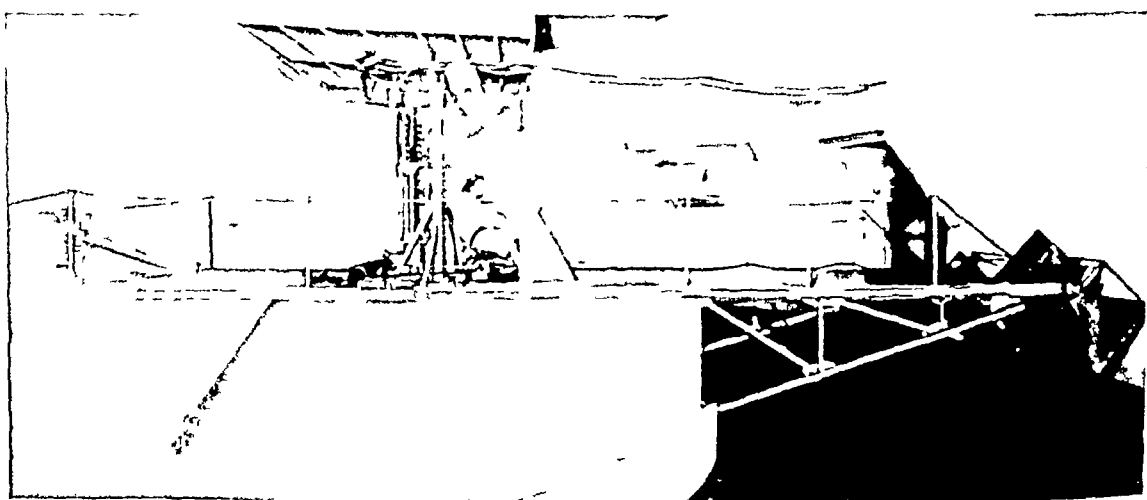


Fig 1 Human centrifuge at University of Southern California in Los Angeles. The subject sits in the gondola or cab at the periphery and the observer at the center. The centrifuge is operated from the control room, one wall of which is provided with a large glass panel looking into the centrifuge room. This gives the operator a satisfactory view of the centrifuge at all times.

duplicate conditions of flight was put into operation at Toronto, Ontario, Canada, in 1941, by the Royal Canadian Air Force (15). Other modern centrifuges were then built in the United States: in 1942, by the Mayo Clinic and Mayo Foundation at Rochester, Minnesota (fig 2) (16), in 1943, by the Army Air Force at Wright Field (fig 3) (17), in 1944, at the Medical School, University of Southern California in Los Angeles (18) under the joint auspices of the Office of Scientific Research and Development and the National Research Council, and, in 1945, a human centrifuge was put in operation by the Naval Air Force at Pensacola. What would have been the most recent of modern centrifuges was under construction at Tempelhof Airfield in Berlin when that city was captured by the Russians. The fact that these research facilities were being extended, even during the closing

stages of the war, indicates the importance which was placed on the problem of centripetal acceleration by our own military leaders and by the German high command.

The effects of centrifugal force on man. The effects of centrifugal force on man are the result of the increased weight of the tissues of the body which the force produces. Since blood is the most mobile tissue in the body, the cardiovascular system is extremely susceptible to changes in man's force environment.

The effects of force on the hydrostatic pressure differences in man's vascular system are shown diagrammatically in figure 4. The ordinates on the left show hydrostatic pressure in millimeters of mercury and, on the right, arterial pressure also in millimeters of mercury. The first figure shows the average position of the pilot in an American fighter plane. The second figure is a schematic diagram of his cardiovascular system at 1 g. At 1 g it can be predicted roughly on the basis of the weight of the blood and the vertical distance between the various parts of the body that if arterial pressure were 120 mm. of mercury at heart level, it would be about 96 mm. of mercury at head level and 170 mm. of mercury at the heels. At 5 g the weight of the blood would immediately increase five times and a five-fold increase would result in hydrostatic pressure differences in the vascular system. Assuming the maintenance of 120 mm. of mercury at heart level, the pressure at the base of the brain would be 0, while at the heels it would be 370 mm. of mercury. Thus, at 5 g, a pressure of 120 mm. of mercury is required simply to lift the blood from the heart up to the head and, on the venous side, a pressure of 250 mm. of mercury would be required

at the level of the heels to return venous blood to the base of the heart

are the most prominent features of the effects of centrifugal force on man, they are secondary to the

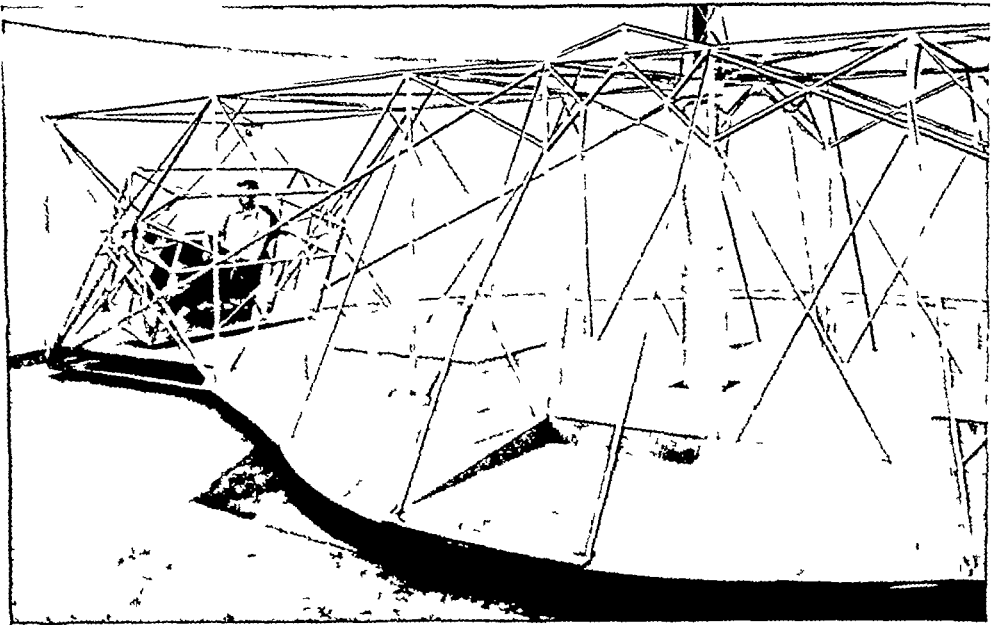


Fig 2 Human centrifuge stripped of recording equipment at Acceleration Laboratory, Mayo Aero Medical Unit. Control room overlooking centrifuge is not shown

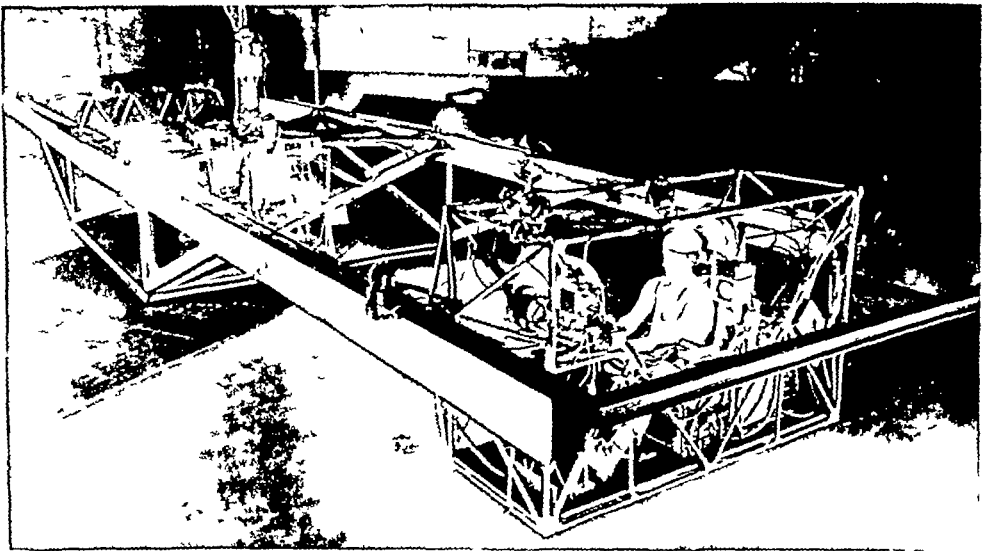


Fig 3 Human centrifuge of United States Army Air Forces at Aero Medical Laboratory, Wright Field

From these considerations it is evident that the ability of man to withstand acceleration is primarily dependent on the cardiovascular system. The nervous system is secondarily involved for although disturbances of vision and consciousness

blood pressure changes and in turn to the effect of these changes on blood flow through the eye and the brain.

From the outset the major requirement for a satisfactory attack on the problem was the

development of instruments which would record quantitatively the cardiovascular variations in man during changing g . Most physiologic recording equipment operates accurately only under a constant environmental force of 1 g and is not satisfactory under conditions of a changing force environment. Hence nearly all human centrifuge instruments had to be developed specifically for use in a centrifuge. As a result of contributions made in all the acceleration laboratories of Canada and the United States, it is now possible to record

The subjective visual changes and loss of consciousness produced in man by sudden exposure to positive acceleration were appreciated before the advent of the modern human centrifuge. Studies on the centrifuge, however, have allowed their more accurate description (26-29) and have conclusively demonstrated that they are results of changes in blood pressure at head level (19, 29, 30). The sudden increase in weight of the blood consequent to exposure to centrifugal force initiates a definite sequence of physiologic events in man.

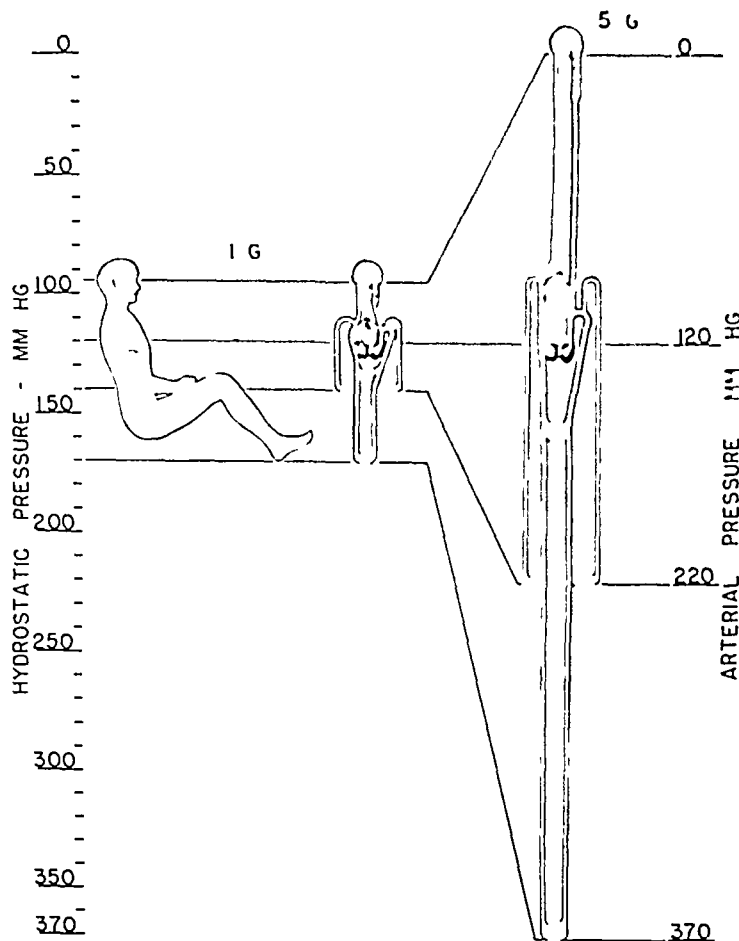


Fig 4 Diagrammatic representation of the hydrostatic pressures in the vascular system of a man in the sitting position at 1 g and at 5 g

continuously and simultaneously, during force environmental changes of 1 to 10 g , man's arterial blood pressure (19), the blood content of his ear (20-22), his ear volume pulse (23), his electrocardiogram, his heart rate (24), his respiration, his intra-abdominal pressure (25) and his reaction time to visual and auditory stimuli. Studies also have been made in which electro-encephalograms, roentgenograms and retinal potentials have been recorded. Besides these, acceleration is routinely recorded and motion pictures of the subject are often taken.

(31) These have been observed in many hundreds of subjects and have been found to be remarkably uniform. The sequence can be divided into two distinct periods: an initial period of progressive failure followed by a period of compensation.

The sequence can best be illustrated by reference to the physiologic recordings made during exposure of a normal subject to 4 g for 15 seconds (fig 5). The arterial pressure was measured by puncture of the radial artery, with the wrist supported at the level of the head. During the first several seconds after onset of the force, the pres

sure fell progressively to 20 mm of mercury. Then some recovery occurred. When the force was terminated, the blood pressure returned to its original level. Correlated with the changes in arterial pressure were changes in the heart rate, ear pulse, blood content of the ear and the subject's response to light signals placed in his peripheral fields of vision.

In all normal subjects so far tested, commencing with the onset of the force a progressive failure occurs. There is decrease in arterial pressure, in

at the moment of onset of the centrifugal force, the resulting pressor reflex does not become effective for 6 to 10 seconds after occurrence of the initial stimulus.

On the average, systolic pressure begins to recover 7 seconds after the force has exceeded 1.5 g. Recovery of amplitude of the ear pulse begins simultaneously. Recovery of the blood content of the ear starts about 2 seconds later and slowing of the heart rate about 3 seconds later. If the recovery of arterial pressure is sufficient, vision also

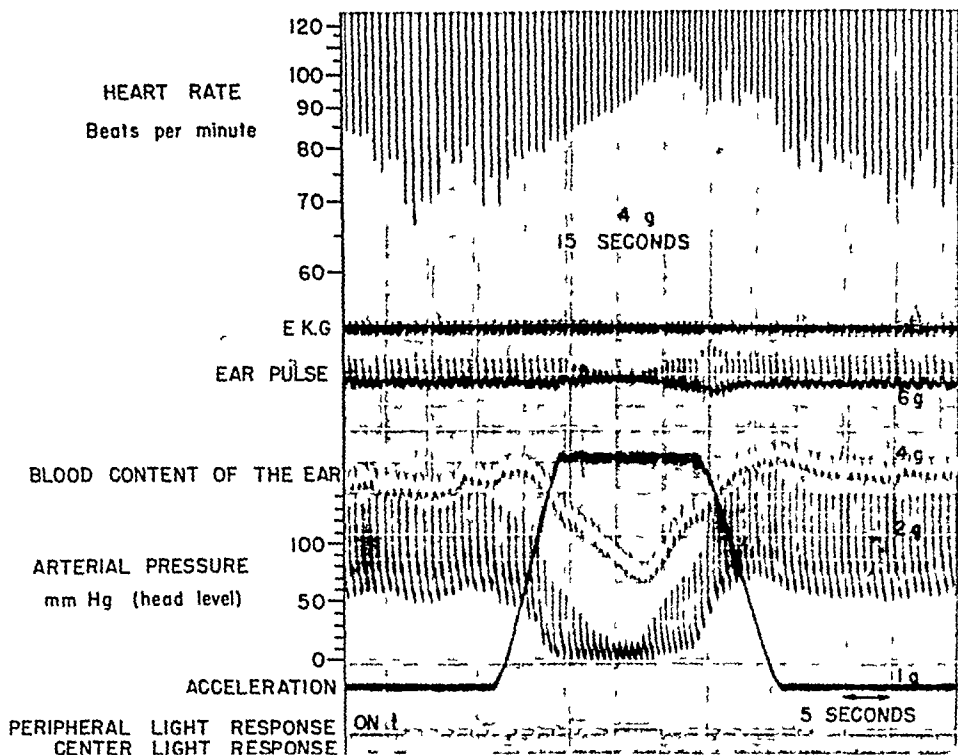


Fig 5 Sequence of physiologic events during exposure of normal subjects to 4 g for 15 seconds. In this and subsequent similar records the vertical white lines are 5 seconds apart. The bottom black line shows the magnitude of the centrifugal force. Notice the initial period of progressive failure during which, in order of occurrence, there are decrease in blood pressure at head level, increase in heart rate, loss of blood from the ear, reduction in amplitude of the pulse in the ear and failure of peripheral vision, then notice a period of compensation during latter half of exposure in which blood pressure at head level rises, ear pulse recovers, blood returns to the ear, heart rate slows and vision is restored.

crease in heart rate, decrease in blood content of the ear and decrease in the amplitude of the ear pulse. Finally failure of vision occurs. In the illustrative instance (fig 5) peripheral vision was lost after a characteristic latent period of 6 seconds. Central vision was maintained. Several seconds after onset of the force, some compensation occurs. Recovery of arterial pressure is generally considered to be due to pressor reflexes initiated by the fall of arterial pressure in the carotid sinus. Although pressure in the carotid sinus falls

is recovered even while centrifugal force is continued.

The fall of arterial pressure at the level of the head is proportional to the magnitude of the centrifugal force to which the subject is exposed. This is illustrated by a series of records obtained from one subject exposed to 2.5, 3.5, 4.5 and 5.0 g (fig 6). In these runs, the systolic pressure at head level, measured in millimeters of mercury, fell to 70, 40, 10 and 0 respectively. The other cardiovascular changes were likewise progressively more

marked Symptoms became successively more severe At 2.5 g, vision was maintained At 3.5 g, peripheral vision was lost after 5 seconds and was recovered after 10 seconds of exposure to the maximum force At 4.5 g, peripheral vision was lost after 5 seconds and central vision after 8 seconds Recovery did not occur until the force was re-

In sharp contrast to the marked decrease in arterial pressure at head level, relatively little fall of pressure occurs at heart level This is illustrated in figure 7 In this experiment, the blood pressure was recorded simultaneously from each radial artery One wrist was supported at head level and the other at heart level The blood pressure at head

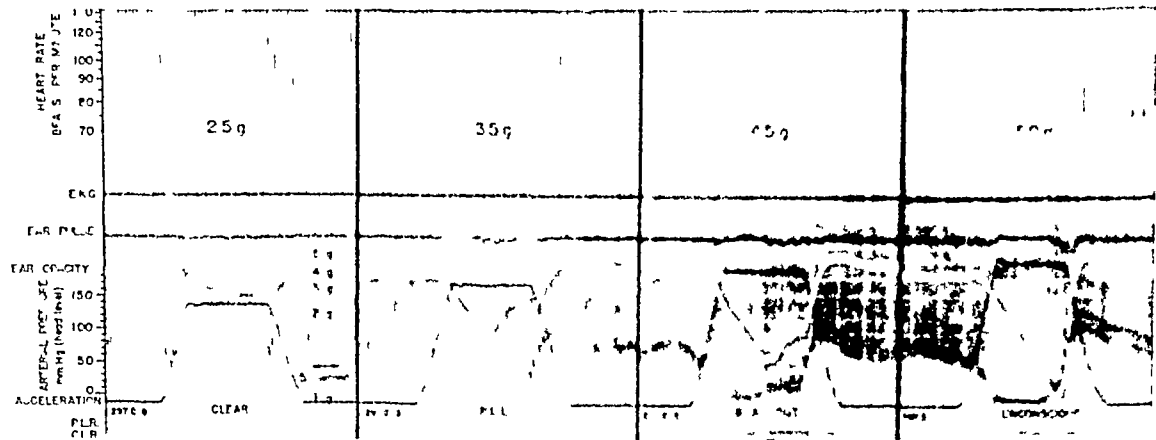


Fig 6 Records showing increasing severity of physiologic changes in man during exposures to accelerations of increasing magnitude (refer to text for full details)

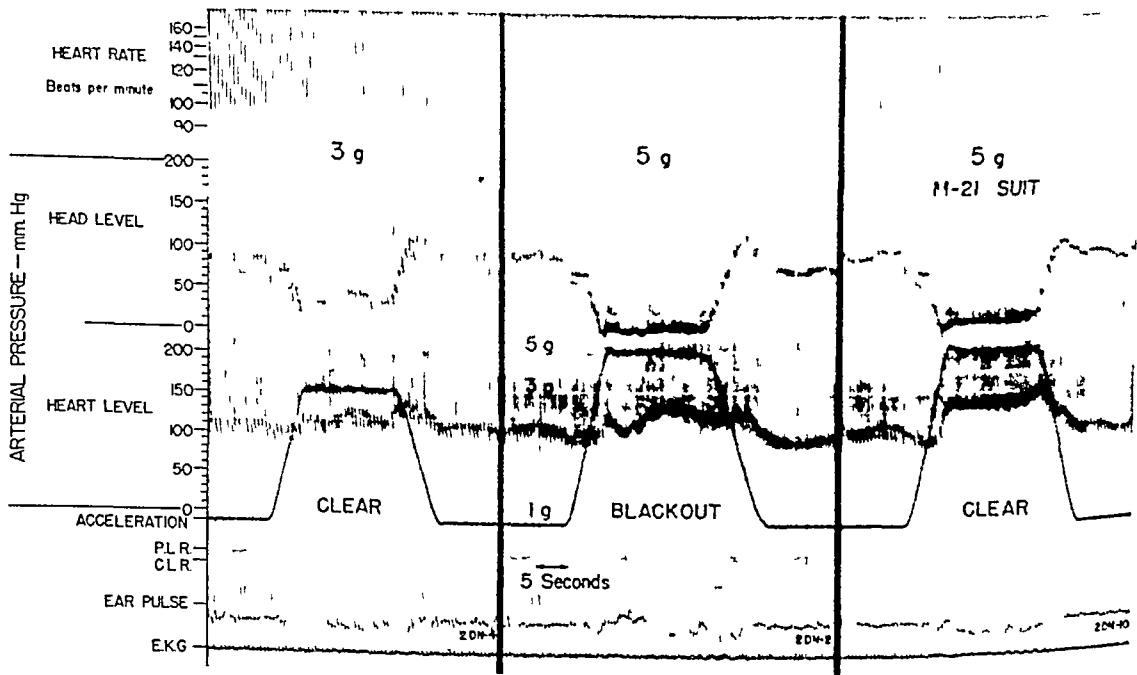


Fig 7 Simultaneous recording of radial arterial blood pressure at the level of the head and at the level of the heart during exposure to 3 and 5 g without protection and at 5 g when using an M-21 pneumatic anti-blackout suit

duced At 5 g, consciousness was lost between the fourth and sixth seconds When consciousness is lost, recovery to the point where the subject just begins to respond to light signals usually requires 15 to 30 seconds, even though the force is terminated with the onset of unconsciousness In about 50 per cent of instances, convulsive seizures occur during the period of recovery (28)

level was markedly reduced, as in the previous experiment Arterial pressure at heart level, however, was maintained within normal limits throughout the period of progressive failure and actually increased to hypertensive levels of more than 200 mm of mercury, systolic, during the period of compensation

It is of considerable physiologic interest that the

hindrance to venous return and the arterial shunting effect produced by centrifugal force were not sufficient to interfere with maintenance of normal blood pressure at heart level in these experiments. On the contrary, in response to the pressor reflexes induced by the fall of arterial pressure at head level, the cardiovascular system was capable of producing marked hypertension at heart level during the period of compensation.

The sequence of changes which has been repeatedly and consistently observed can be summarized as follows:

(1) Acceleration increases the weight of blood and tissues.

(2) The increased weight of the blood reduces blood pressure at head level to such a degree that disturbances in vision and consciousness may occur.

(3) The decrease in arterial pressure at head level initiates pressor reflexes which become effective in about 7 seconds. The resulting increase in arterial pressure at heart level is usually sufficient to produce some degree of recovery at head level even though the force is maintained.

The changes in blood pressure are the key to the orderly pattern of changes in ear opacity, ear pulse and heart rate. These simply reflect the alterations in blood pressure. They have, however, afforded simple routine methods for following the cardiovascular effects of acceleration in man. Use of these recordings and elucidation of the orderly and uniform sequence of physiologic events, have afforded an objective measure of man's g tolerance. They also have allowed the development of an accurate bio assay method for the quantitative estimation of the protective value of any device or procedure designed to offset the effects of positive g (32). In this bio assay, as in other assays, it is essential that conditions within, and surrounding, the test object, in this instance a human being, remain constant if satisfactory quantitative determinations of protection are to be obtained (33). The problem of protection becomes, in physiologic terms, How may the sequence of events in man be altered so as to reduce or eliminate the period of progressive failure?

There are three general methods which can be used to increase man's ability to withstand centrifugal force. These are:

- 1 Limiting the duration of the force
- 2 Postures or positions which reduce vertical hydrostatic distances
- 3 Procedures which increase blood pressure

By limiting the duration of the force to a period less than the usual latent period of about 4 seconds required for the development of symptoms, pilots can avoid the physiologic consequences of exposure to centrifugal force. This procedure is frequently used by pilots when they are required to

test the performance of planes at high g forces. The circumstances are illustrated in figure 8. The subject studied lost consciousness after about 7 seconds of exposure to 6 g. However, by limiting the duration of the force he withstood 7 g for 3 seconds and 9 g for 1 second with only transient dimming of vision. The maneuver requires precise estimation of the duration of the force. When the exposure at 7 g was prolonged from 3 to 5 seconds, consciousness was completely lost. At high speeds, the method is dangerous since the pilot, to shorten the duration of the force and yet complete a turn, must use violent maneuvers and hence may overstress his plane. Furthermore, should he underestimate the duration of the force and hold the g beyond his symptom latent period, unconsciousness would result.

Changes in the position of the pilot can be used to shorten the hydrostatic distance between the various parts of the body. In the prone or the supine position, the vertical distance between heart and head is zero and centrifugal force does not reduce the arterial pressure at head level. In this position, man can withstand maintained forces in excess of 12 g without occurrence of visual symptoms (13, 34, 35). The practical difficulties of flying a plane in the prone or supine position are numerous, although many have been overcome by mechanical aids, the most recent and satisfactory of which have been developed at the University of Southern California (36).

The possibility has been investigated of accomplishing partial reduction of the hydrostatic distance between head and heart by having the pilot's seat tilt backward at an angle of 45° to 60° (11, 36, 37). This was found to be an effective means of increasing g tolerance but was not found practical in conventional aircraft. On the other hand, pilots are able to accomplish some reduction in heart-brain distance by crouching forward in their seats. This procedure was used extensively by German pilots (1, 9). While all of these postures effectively increase g tolerance, the necessity for the pilot to assume an abnormal position to avoid blacking out restricts his activity in the cockpit and, as a rule, decreases his efficiency in combat.

Procedures of which the effectiveness is based on increasing the blood pressure during exposure to positive acceleration were widely used to prevent blackout during World War II. Of these procedures, self-protective maneuvers utilizing the voluntary musculature and simple suits which apply pressure to the dependent portions of the body have been of the greatest practical value. The efficacy of certain drugs which have a pressor effect has been investigated (38, 39), they have not been used as a practical means of increasing g tolerance.

Self-protective straining maneuvers of various types undoubtedly have been used by pilots more

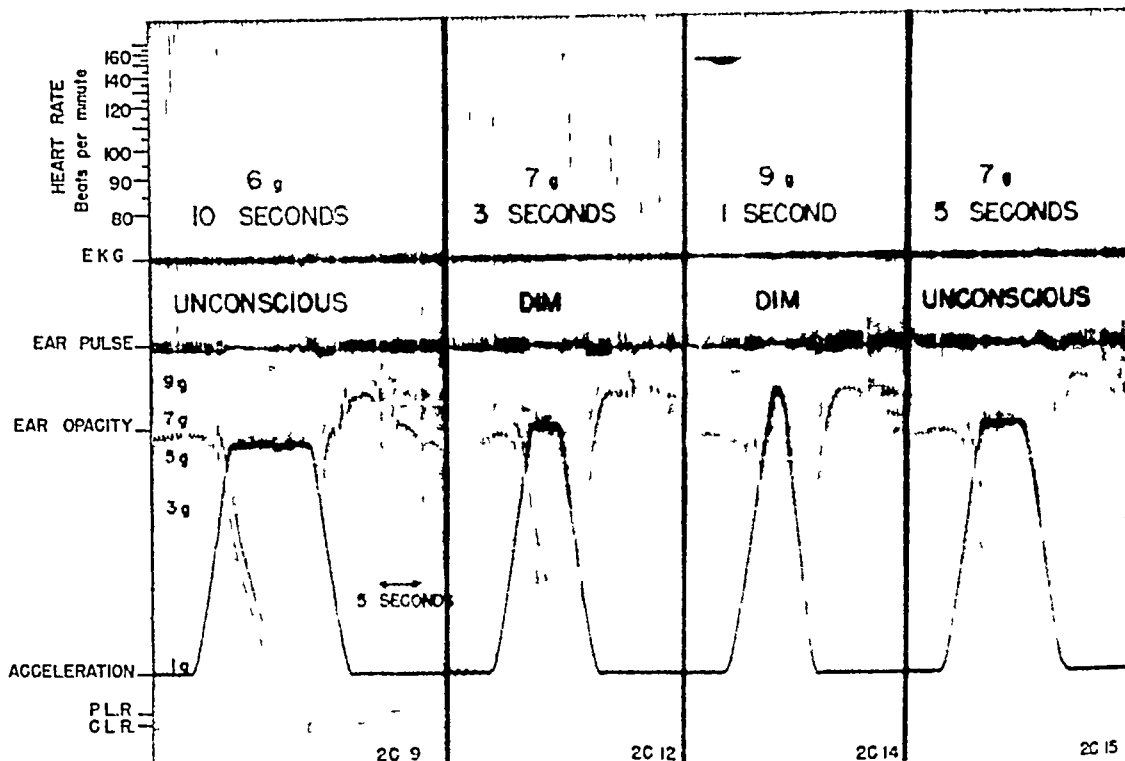


Fig 8 Interruption of the sequence of physiologic events by short exposures to g. Subject rendered unconscious by exposure of 10 seconds to 6 g withstands 7 g for 3 seconds and 9 g for 1 second with only dimming of vision, but loses consciousness again when the exposure at 7 g is increased to 5 seconds

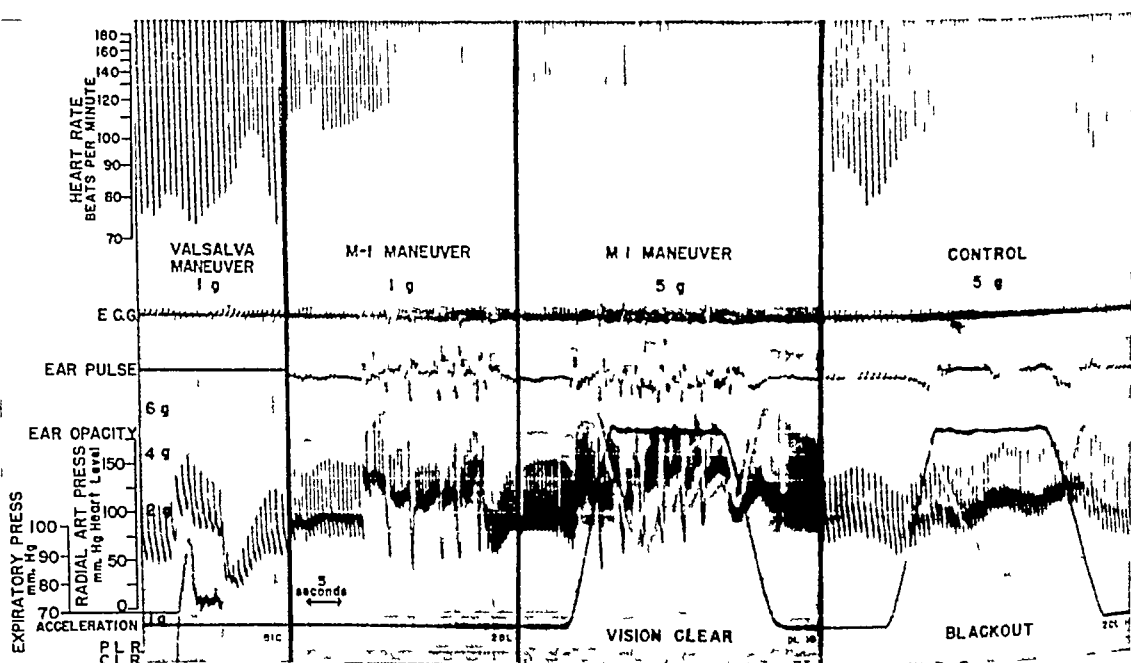


Fig 9 The effect of the M-1 maneuver on g tolerance and arterial blood pressure at heart level. Notice that the maneuver raised the blood pressure and that this hypertension enabled the subject to withstand 5 g without reduction in vision or loss of ear pulse while, at 5 g without performing the maneuver, the subject lost his ear pulse and blacked out

than any other single procedure or device to prevent blackout. The most effective self-protective maneuver thus far developed is the so-called M-1 maneuver (40). It consists of a series of forced ex-

pirations through a partially closed glottis, coordinated with muscular straining. The effect of the maneuver on blood pressure at heart level is shown in figure 9. At 1 g the maneuver produced a

sustained elevation of arterial pressure. At 5 g the effect on blood pressure was similar and was maintained for the duration of the exposure to the force. This degree of hypertension at 5 g was sufficient to maintain clear vision. Without performance of the maneuver, normal blood pressure at heart level was maintained at 5 g, this, however, was insufficient to maintain circulation to the head and vision was completely lost. Observations similar to those just recounted have been made on a large number of individuals. By proper use of the maneuver, many have been able to maintain clear vision during sustained exposures to 9 g. The performance of straining to prevent blackout, while effective, has the disadvantage that it decreases

A similar device was featured in the Hollywood production, "Dive Bomber," in 1941.

Prior to the war and the advent of the modern human centrifuge, the most important factor limiting man's capacity to withstand centrifugal force was generally believed to be hindrance of venous return to the heart from the dependent portions of the body. This concept led to the development of various hydrostatic and complicated pneumatic devices which applied gradient pressures to the body with the intention of preventing pooling of blood below the heart.

The Franks flying suit, developed by the Royal Canadian Air Force at the outset of the war, was an outgrowth of this general concept (42). It is



Fig 10 Early anti-blackout device developed under auspices of United States Navy, consisting of abdominal corset with bladder inflated by hand bulb pump

the pilot's efficiency and increases his fatigue. These objections do not apply to mechanical, automatically controlled, protective devices such as anti blackout suits.

The development of anti blackout suits. The United States Navy began its initial studies on anti blackout devices as early as 1932 (41). Before 1938, in co-operation with a corset manufacturer and several physiologists, it developed a pneumatic abdominal bladder, incorporated in a corset arrangement similar to that shown in figure 10. The pilot inflated the pneumatic bladder with a hand bulb prior to anticipated exposure to force. The device was designed to overcome the pooling of blood which is believed to occur in the splanchnic vessels. This arrangement, although not generally accepted, was used by a few test pilots



Fig 11 The Franks flying suit (FFS) developed by the Royal Canadian Air Force. In this suit a gradient pressure is provided by water which, in the amount illustrated, is placed within the bladder system of the suit.

shown in figure 11. The bladder system of this suit is filled with water. During exposure to force, the weight of the water is increased just as is the weight of the blood, therefore, the suit applies an external gradient pressure to the body, equal and opposite to the pressure generated in the venous system. This suit became the first anti blackout device to be put to use in combat.

A pulsatile pressure suit was developed by the United States Navy (43) in 1941 (fig 12). This suit was designed to apply repeated waves of air pressure to the extremities, progressing from the ankles and hands toward the trunk, in order to milk the venous blood back to the heart. Only a few models of this suit were built. The complexities of the suit and its inflating mechanism discouraged its use and further develop-

A pneumatic gradient pressure suit was developed under the auspices of the United States Navy (14) and received flight tests in 1912 (fig. 13). This suit was designed to accomplish the same pur-

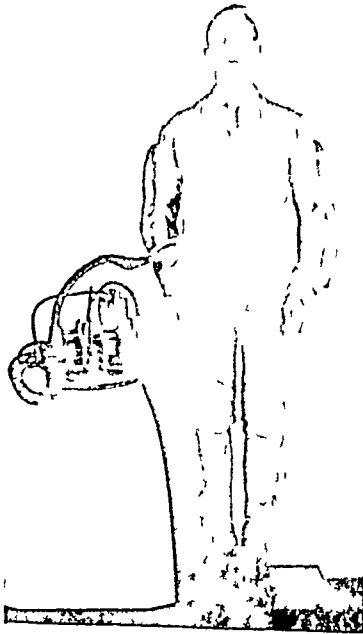


Fig. 12 Pulsatile pressure anti blackout suit and valve designed by United States Navy

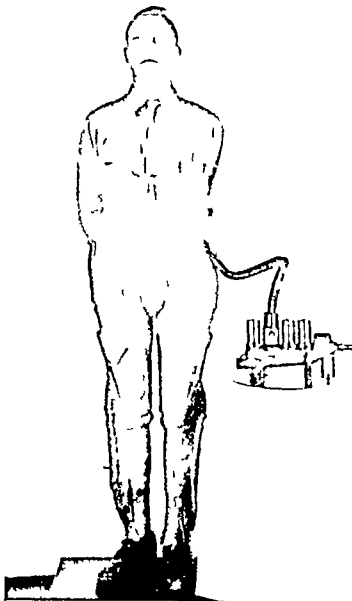


Fig. 13 The pneumatic gradient pressure suit (GPS) and valve designed by United States Navy and used briefly by the United States Army Air Forces (AAF G-1 suit)

pose as the water suit, the pressure gradient being pneumatic instead of hydrostatic. The gradient pressure suit was given trial in combat by both the United States Navy and the United States Army in 1943 and, with some modifications, was

adopted and used briefly by the United States Army as the AAF G-1 suit.

A similar but somewhat more complicated, pneumatic gradient pressure suit had been made independently by Australian workers (15). It was tested on their centrifuge in 1941. The Australian suit and its accessories weighed more than 50 pounds. It was not put to practical use.

All of the suits described were tested early in the war in aircraft, some in combat, and were found to provide protection against blackout, but because they were complex, cumbersome and uncomfortable, they were not generally accepted by pilots. They did, however, demonstrate the desirability

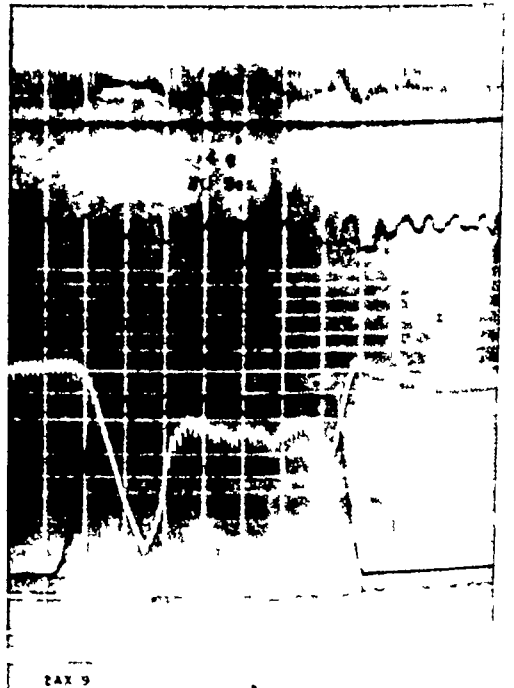


Fig. 14 Thirty seconds' exposure to 4 g. Notice that the condition of subject did not progressively and continuously decline, as might have been anticipated had venous return been a critical factor. Instead, ear pulse and ear opacity recovered after an initial brief period of failure.

of providing anti-blackout protection for pilots and thus stimulated further development of suits.

In 1942, physiologic recording of man's reactions to g, such as those illustrated in figure 14, were obtained on the human centrifuge. This figure shows a 30 second exposure to 4 g. It is evident that the individual was in his worst physiologic state during the first few seconds of the exposure, when there was a pronounced reduction in blood content of the ear and the ear pulse and peripheral vision were lost. After this initial period of failure, ear pulse and vision were restored and the blood content of the ear returned almost to its control level. Had pooling of the blood below the heart been a critical factor, recovery to this extent hardly could

have occurred. The accumulation of blood below the heart presumably would have continued throughout the exposure to g and, if this had been the chief factor limiting the subject's tolerance to g, sustained recovery, to the degree illustrated, certainly would not have been expected. When these findings were uniformly observed in normal subjects, attention was directed from the venous to the arterial side of the vascular tree. A radical departure in design of anti blackout suits followed. Very effective anti blackout suits were constructed which, by applying arterial occlusive pressures to the extremities and pressure to the abdomen, increased the blood pressure at heart level and directed cardiac output towards the head.



Fig 15 Simple arterial occlusion suit (AOS) consisting of cuffs about the extremities which occlude the circulation and an abdominal pressure bladder which directs blood flow to head

during critical periods of exposure to centrifugal force.

A simple arterial occlusion suit of this type is illustrated in figure 15 (46). It consists of a pneumatic abdominal bladder and four pneumatic cuffs encircling the proximal portions of the extremities. With the onset of centrifugal force, the cuffs are inflated to pressures which occlude the circulation.

A progressive arterial occlusion suit is shown in figure 16 (47). The legs of this suit contain a series of transverse bladders connected by small orifices. The suit is inflated from the ankles so that an arterial occlusive pressure wave, progressing from the ankles upward, is produced.

Suits of the arterial occlusive type afforded approximately 3 g protection in centrifuge tests as compared to the 1 to 1.5 g protection afforded by the hydrostatic and gradient pressure suits. Al-

though arterial occlusive types of suits virtually eliminated blackout in aircraft, they were not generally acceptable to pilots. Actually, much more protection was provided than was required and the pilots objected to the discomfort caused by the high pressures necessary to obtain this high degree of protection.

At this stage in the evolution of anti g suits, the following became apparent:

1. On the basis of field trials (42, 48) and combat reports (49-51) an anti blackout suit which increased g tolerance by as much as 1 to 1.5 g was adequate for pilots of fighter aircraft then in use. With this degree of protection, blackout was practically nonexistent in combat maneuvers.

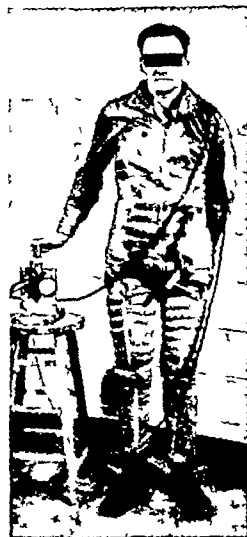


Fig 16 Progressive arterial occlusion suit in which arterial occlusion pressures were applied from the ankles upward

2. To be of practical value, the suit must be simple and comfortable and must be acceptable to pilots.

All anti blackout suits had in common the application of pressure to the regions of the body below the heart. Whether originally designed to affect, primarily, the venous or the arterial circulation, their ultimate effect was to increase arterial blood pressure. Centrifuge studies then served to elucidate the essential factors in design of suits. The following facts were found:

1. Protection afforded by immersion in water (fig 17) was limited (52) and, while water suits did afford 1 to 1.5 g protection, the same and greater protection could much more easily be provided by application of air pressure. Also, it was found that water did not apply its highest pressures to those regions which produced the greatest protection.

(53) Hydrostatic gradient pressurization, therefore, was abandoned

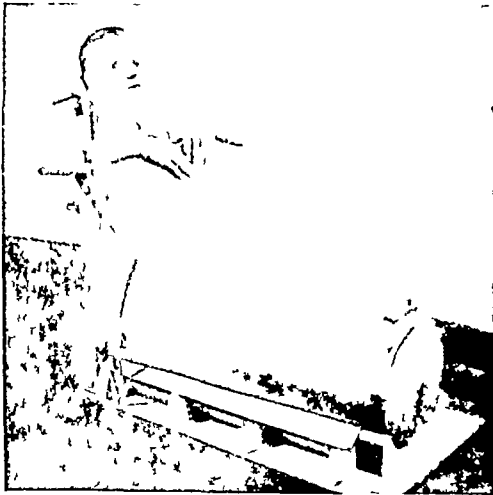


Fig 17 Bath tub used on human centrifuge to test the effect of immersion in water on g tolerance of man

was determined primarily by its size and the pressure to which it was inflated (53)

1 Although it was important to apply pressure to the legs the amount and distribution of this pressure was not critical (53)

Various simplifications of anti blackout suits followed establishment of these findings. The army modified the complicated gradient pressure suit to a simpler single pressure suit (AAM G 2) (55). L import and Herrington (56) developed a single pressure pneumatic lever suit. Wilkins (57) with a revolutionary design applied counter pressure by a net suspension suit.

Another simultaneous line of development which had as its basis the findings enumerated above, led to the evolution of a simple pneumatic bladder system in which the calf, thigh and abdominal bladders were constructed in a single unit designed to be inflated to a single pressure (fig 19) (53). This simplified single pressure bladder system could be built into any type of garment which would allow reasonable transmission of the blad

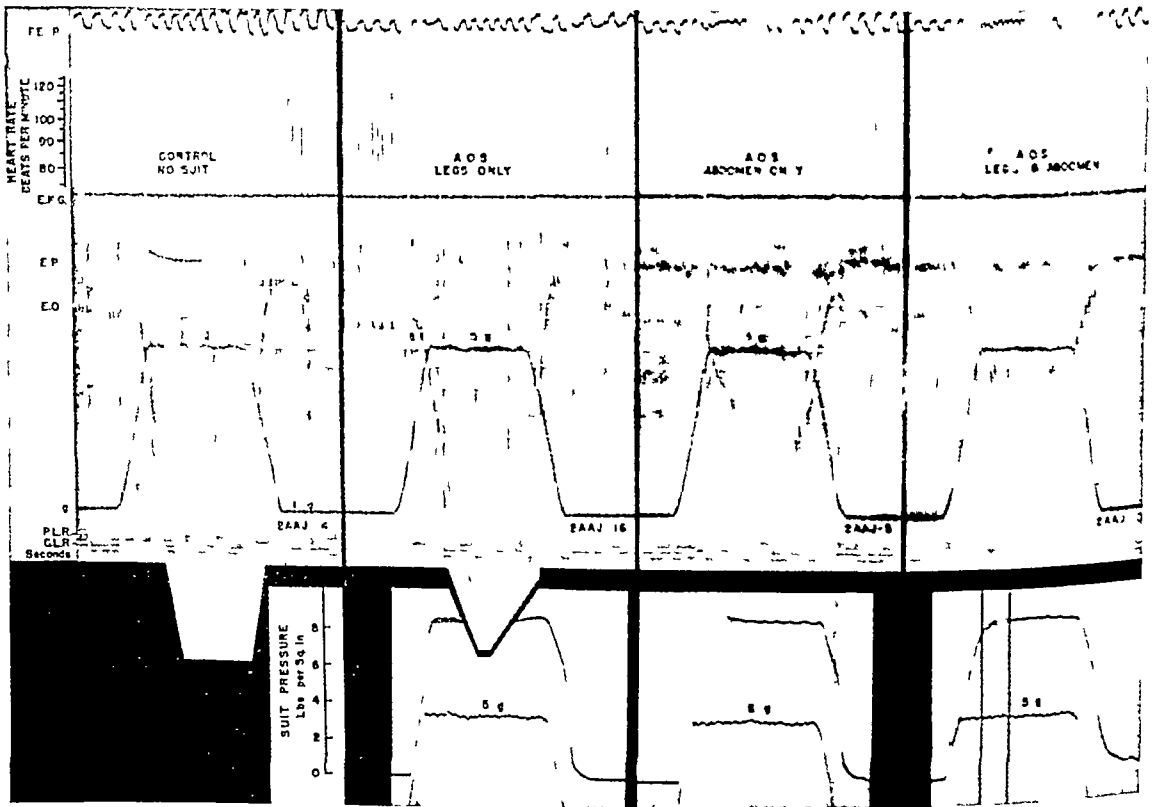


Fig 18 Analysis of protective value of component parts of anti-blackout suit. Figure illustrates the protection obtained by pressurization of legs only, abdomen only and legs and abdomen together

2 Pressurizing a suit to a gradient pressure had no detectable advantage over a single pressure (54, 55)

3 The abdominal bladder was the most important component of the anti-blackout suit (fig 18) and the amount of protection afforded by a suit

der pressure to the body. It was demonstrated that, on inflation to suitable pressures, the simplified bladder system prevented the occurrence of blackout in the majority of pilots flying combat aircraft (58)

The navy put this bladder system into a flight

coverall (United States Navy Z 1 and Z 2 suit) in 1944 (fig 20) (59) The army put the same blad-



Fig 19 Simple single pressure bladder system which provided protection when built into garment, allowing transmission of bladder pressure to body

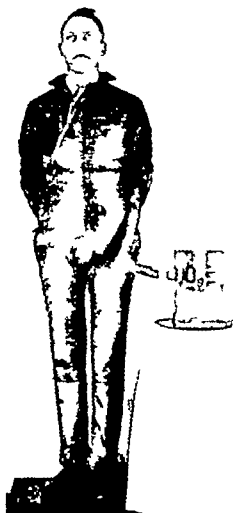


Fig 20 Anti blackout suit coverall incorporating simple single pressure bladder system used by United States Navy (called Z-2 suit in navy and G-4 suit in army)

der system into a skeleton type suit (AAF G 3 suit) designed to be worn over the pilot's regular

uniform (fig 21) (60) These suits weigh less than 3 pounds and are as comfortable to wear as conventional flying clothing. Similar suits then were developed at the Royal Canadian Air Force Acceleration Laboratory at Toronto and at the Royal Air Force Laboratory at Farnborough, England.

The protection against blackout afforded by these suits is due to the increase in blood pressure at heart level which they produce and which is available during exposures to centrifugal force for the maintenance of circulation to the head (61). Inflating the suit at 1 g produces an immediate increase in blood pressure which is well sustained for the duration of the inflation. This increase in

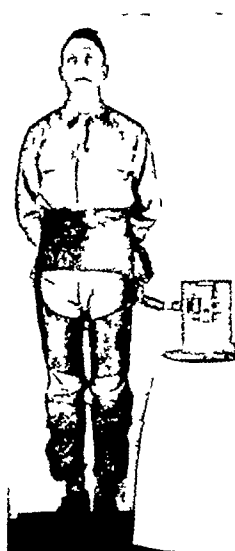


Fig 21 Anti blackout suit cut away garment incorporating simple, single pressure bladder system used by United States Army (called G 3 suit in army and Z 3 suit in navy)

blood pressure tends to be greater the higher the pressure to which the suit is inflated.

The effect of the suit on arterial pressure at 5 g is illustrated by an experiment in which blood pressure was recorded simultaneously from one radial artery, with the wrist supported at head level and, from the other with the wrist supported at heart level (fig 7). At 5 g, without the suit blood pressure was maintained at a normal value at heart level but this was insufficient to maintain circulation to the head. Pressure at head level fell to zero during the first 7 seconds of the run and vision was completely lost. Inflation of the suit at 5 g produced immediate hypertension at heart level, which was sufficient to maintain circulation to the head during the exposure so that vision was maintained.

Anti-blackout suits of this simplified type were rapidly accepted by fighter pilots. In the last years of the war, these suits were issued to army and navy fighter pilots as rapidly as manufacture of the suits and suit pressure control valves would permit. Combat reports gave conclusive proof that these suits afforded our pilots a definite margin of superiority.

It is interesting to note that German scientists apparently were unaware of the real effectiveness of anti-blackout suits although they did appreciate many of the physiologic principles of anti-blackout devices (1, 9, 11, 12). As far as can be told from information at present available, the only anti-blackout procedures they actually advised during the war were the crouch and reclining positions. It is now known, however, that in the closing phases of the war pneumatic anti-blackout suits copied directly from models captured from the Allies were in preliminary stages of production in Germany (62). The Japanese, as was true also of German scientists, had human centrifuges available for detailed study of black-

out (62). The only anti blackout procedure they are believed to have used however was taping of the extremities and trunk of the body to prevent pooling of the blood in these regions. Early in the war, tests performed at the United States Army Air Forces Aero Medical Laboratory indicated that this time consuming and uncomfortable procedure increased g tolerance by only 0.5 to 1.0 g (63).

Anti blackout suits, especially simplified suits used by our air forces, are not the answer to the problem of prevention of blackout among aviators. Since in any given turn centrifugal force is proportional to the *square* of the velocity, it can be predicted that, with the advent of super speed planes, the present anti blackout suits soon will be as obsolete as the planes in which they were used. Additional physiologic investigations will be necessary before methods can be developed which will enable pilots to utilize the full potentialities of the new aircraft.

ACKNOWLEDGMENTS AND REFERENCES

Unfortunately, in this paper it has not been possible to refer directly to reports dealing with a great deal of the work carried out during the war on the effects of acceleration in man. Although the subject has been declared "open" by military authorities, most workers have not yet published their data in standard journals. This has made it extremely difficult, if not impossible, to compose an accurate review and to indicate the correct sources of the data used. Reference only to published work would have allowed discussion of only a small part of the total accomplished. Therefore, in some instances, as a substitute for a standard type of bibliographic reference, and as a means of acknowledging and indicating the sources of the information used in the text, the names of those believed responsible, with the years and the laboratories in which the information was accumulated, are given below. Such a procedure, by its very nature is full of inaccuracies and for these, and for the many omissions which must have occurred, the authors offer their apologies.

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CLOTHING AND HEAT EXCHANGES

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Ever since the days of Rubner, the heat exchanges of man with his environment have been the subject of intensive study. In this century, a great body of detailed knowledge has resulted from the work of groups headed by DuBois, Yaglou and Houghten, Winslow, Gagge and Herrington, Dill and co-workers, Murlin, Sheard and his associates, as well as from individuals such as Bazett, Adolph and Hemingway. Abroad we have had the outstanding work of Bedford in England and of Lee in Australia.

However, all this work has been *intensive* rather than *extensive* in scope. Subjects were generally naked or lightly clad. Environmental conditions did not extend much beyond the narrow range of temperature maintained in modern homes in the temperate regions. This does not of course apply to the work that had been done in tropical conditions by several expeditions. Yet physiology is concerned with the maintenance of the "milieu intérieur" necessary to life in the face of wide fluctuations of the external environment. Adjustments that are purely physiological suffice only for a limited range of external fluctuation. Outside this range, man, to live, must create his own "milieu intermédiaire" by the use of clothing, a tent or a house. In the proper study of this field between pure physiology and physics, knowledge of physiology is needed just as much as understanding of physics.

Yet the manner in which clothing could affect the heat exchanges of man in the environments in which some men have to live and work had not

been studied scientifically to any great extent, and not by physiologists. Clothing has been taken for granted so long, each of us feels he is an expert. Almost without exception the design of clothing has been dominated by the whims of fashion or by commercial considerations. *Functional design*, based on the functional requirements, was almost completely unknown.

The outbreak of modern warfare brought, to us in 1939, a challenge to the physiologists that could not be refused, a challenge that we surely should have foreseen and been prepared to meet. Airmen must remain efficient in gun-turrets, which were impossible to heat adequately, in the stratosphere where the external temperature was 55° C below zero. The Navy would have to operate in the extremes of cold, wet and wind of the North Atlantic. Ditched aircrew and shipwrecked Naval personnel would be adrift in small rubber dinghies or open boats in direct contact with the elements. Driving a tank, even in weather that might be described as mild, is an astonishingly cold job. Our armies might have to fight campaigns where exposure to cold was as great an enemy as the human foe. On the other hand, the campaign in North Africa called for study of how to maintain men in the dry heat of the desert, and the war against Japan in the humid heat of the jungle. Actually experience has now taught us, in more than one costly lesson, that it was the less dramatically extreme conditions, of moderate cold with constant exposure to moisture, that posed the greatest problems. I

few that those of us working in this field failed, if not in appreciating this ourselves, at least in convincing the authorities of it. Had we done our job better, much hardship of our troops in "Sunny Italy" could have been avoided, as well as in the Aleutians or elsewhere. Figure 1 is adapted from Dr. DuBois' lectures, and will serve to remind you of the factors involved in the heat balance. Unless the two sides of the heat equation remain equal, a *Heat Debt*, positive or negative, will develop. "Heat Debt" is exactly analogous to "Oxygen Debt" so familiar to physiologists. Thus if we are to provide adequate clothing insulation for men on a given military mission, we must first know the average metabolic rate.

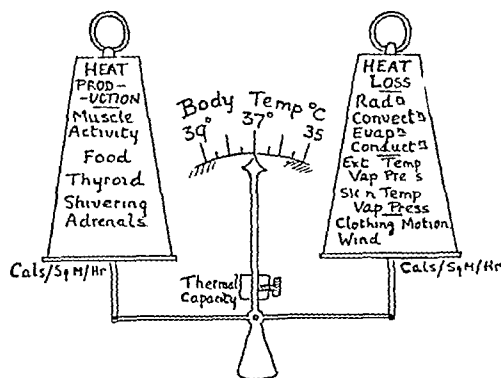


Fig 1

involved. For a pilot sitting at his task it will be not more than 50 Cals/Sq M /Hr. For an infantry man the average rate may be much higher. The calorific value of the daily rations will be some guide. Each specific military problem requires careful investigation of these factors.

Clothing affects the right hand side of the balance—the heat loss, and the first step was to find a unit of measurement in which to measure its effect. Different groups interested in heat exchanges use different units, the heating and ventilating engineers use B T U per minute and °F, the physicists calories per second and °C, the physiologists kilocalories per hour and usually °F. There seemed room for a new unit, convertible to any of these by numerical factors, but in addition carrying some concrete meaning to the layman. Collaboration between three groups of workers led to the introduction of the "Clo unit" of thermal insulation.

Thermal insulation is a "resistance" unit and like all such "resistances" is given by the ratio of the driving force, here the temperature difference,

to the flow per unit area of cross-section, here of heat, that results.

Thus— Thermal Insulation

$$= \frac{\text{Difference of Temperature}}{\text{Heat flow per unit area}}$$

$$\text{Total Insulation (Clothing + Air)} = \frac{T_{\text{Skin}} - T_{\text{Air}}}{\text{Cals/Sq M/Hr}}$$

and by definition—

$$1 \text{ Clo} = 0.18 \frac{\text{OC}}{\text{Cals/Sq M/Hr}}$$

$$= 0.88 \frac{\text{OF}}{\text{B T U /Sq Ft /Hr}}$$

The Clo unit is, of course, *defined*, without any scientific uncertainty, in terms of the preexisting physical units, by the numerical conversion factors. But the usefulness of the new unit, and the reason for its introduction, lies in the example given below.

"One Clo unit of thermal insulation in clothing suffices to keep a sitting-resting subject (Metabolic rate 50 Cals/Sq M /Hr) at 70°F (21°C), Relative Humidity less than 50%, air movement 20 ft/min (10 cms/sec or "still air") indefinitely in a comfortable steady state."

We found that we could explain even to a General or Admiral, without a course in physics for which he had neither time nor patience, that his uniform had about One Clo unit of thermal insulation, his greatcoat another one Clo unit, and that together they provided him with a total of Two Clo units. With some pictograms, as figure 2, we could convince him of the importance of the metabolic factor. The "Met" is another convenient practical unit, of metabolic rate. 1 Met stands for a rate of 50 Cals/Sq M /Hr, the usual "resting" value. Level walking will be a metabolic rate of about 3 Met. The pictogram of figure 3 was used to convince the lay authorities that this scientific study had some important practical results. Six 11 Clo sleeping bags are much heavier and bulkier than six 8 Clo sleeping bags and it may be sounder logistics to take some stoves and the lighter bags.

The total thermal insulation of a clothed man is the sum of three components (fig 4). The insulation of the tissues is controlled by the peripheral circulation with the limits as shown. We shall see that it is difficult to provide more than 4 or 5 Clo units in the clothing. The insulation of the air depends on the degree of air movement, and by a fortunate physical coincidence, we can use standard tables for this that apply approximately whether the temperature is -40°F or +40°F. Unfortunately we still do not know how

to translate movements of the body, as in walking into an equivalent rate of air movement. Thus, given the external conditions of the problem, temperature, wind and so on, and the activity of soldiers, it is a matter of simple algebra to calculate the required insulation in Clo units. Too often the difficulty was in obtaining the data of

search Councils and the Research Divisions of the Services and guided by Sub Committees on Protective Clothing under the leadership of Doctor Newburgh in the U. S. and Doctor Hall in Canada. The Clo determination (as it was called) was widely made. Some lost faith in it because of its great inherent difficulties. Unless the temperature is such that a steady state near that of comfort is established, i.e. the insulation is adequate, a large heat debt accumulates, and we cannot calculate this with any accuracy, what ever formula for mixing rectal and skin temperatures we adopt to obtain the average temperature of the body. I have always contended that there is no point in planning a Clo determination at temperatures other than those where the heat

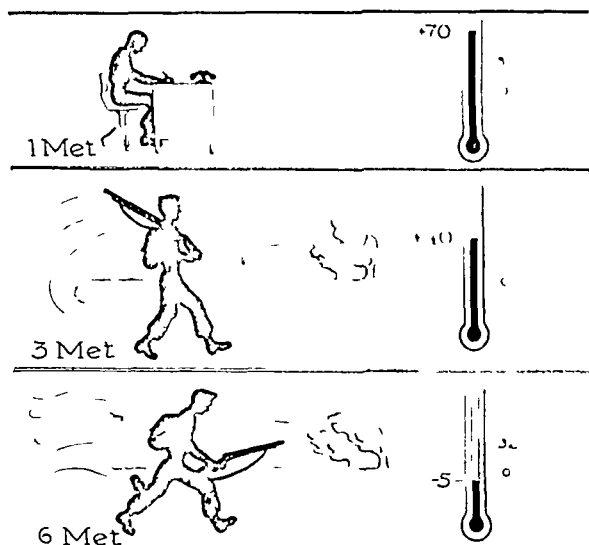


Fig 2 What 1 Clo unit is good for

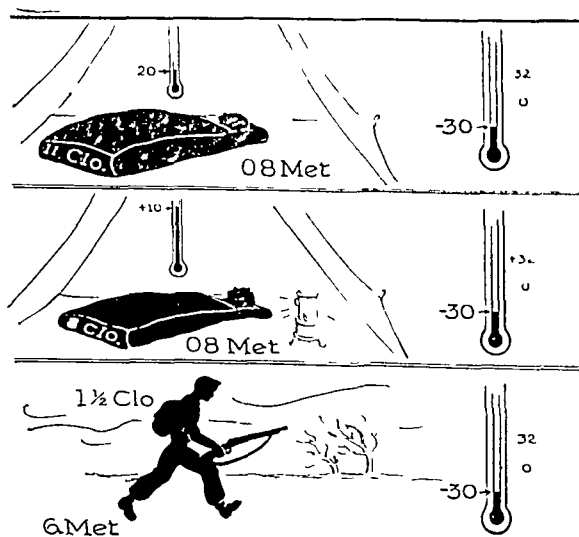


Fig 3 How many Clo units needed?

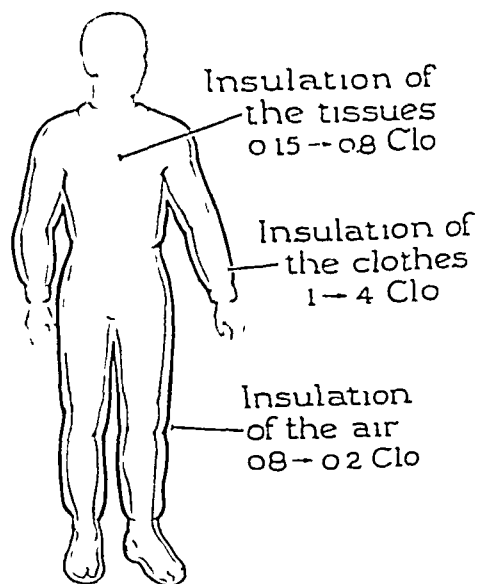


Fig 4

debt is small, however informative experiments in extreme conditions may be in other respects. The issue is dodged by the use of an "artificial man" (fig 5) where physiological variations are conveniently absent, and any heat debt is voided by keeping, automatically, the body temperature constant and measuring the heat required to do so. This artificial man of figure 5 has historical interest only, as I think it was the first, built in Toronto. His offspring have been better equipped with limbs and with accuracy. The factor of body moisture is absent in most models.

The preliminary work in cold chambers revealed results that were unsuspected from the classical study of heat exchanges of lightly clothed men. Figure 6 shows the averaged results on 50 subjects seated in heavy flying clothing in the cold chamber. The deep body temperature fell rapidly to levels far below those ever seen in experiments in lightly clad subjects, where the metabolic response

requirements, and here the Climatologists, such as Siple, did sterling work in the O. Q. M. G., and devised many charts by which the clothing and equipment required for any mission, whether to Tibet or Alaska or Malaya, can be reliably laid down.

Cold chambers at the R. A. F. medical section, Farnborough, and the R. C. A. F. in Toronto, were the precursors of many that mushroomed forth, under the stimuli of our respective National Re-

occurs before the rectal temperature has fallen more than 2 or 3 tenths of a degree. In heavy clothing the physiological response of increased metabolic rate (shivering) is delayed until the third hour, when the subjects become quite suddenly miserably cold. The normal response of vasoconstriction is also markedly inhibited until

The heavily clothed, inactive, man is therefore physiologically ill equipped to maintain body temperature, and some measurements of body temperature on aircrew on actual patrol missions showed considerable falls of body temperature. An important question is whether or not this is of any practical consequence. In a series of little known but very important tests on psychomotor efficiency, Dr. Kitching showed that there was a considerable deterioration of performance. The decrease in efficiency was correlated more with the discomfort that ensued than directly with the fall of deep body temperature.

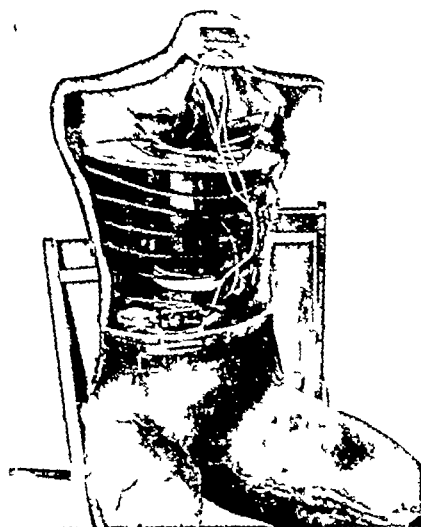


Fig 5

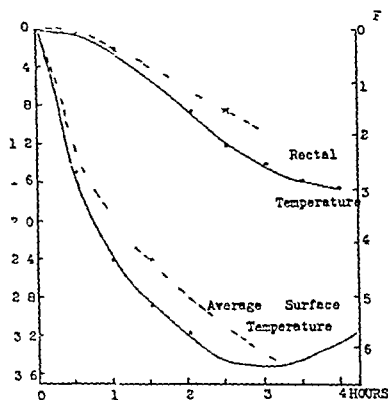


Fig 6 Fall of body temperatures in flying clothing of 2 to 2.5 Clo at 0° to 10°F (Broken lines—3.0 Clo)

the late stages, presumably because the stimulus of rapid fall of skin temperature is lacking. At still colder environmental temperatures, especially with wind, stimulation of the exposed areas, such as the face, brings prompt physiological response of shivering and vasoconstriction, and these remarkable falls of deep body temperature are not seen.

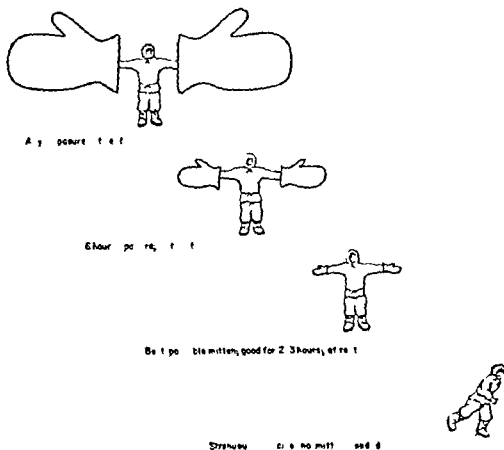


Fig 7 Relative size of mittens needed for different exposure times at -20°F

All this work can be summarized by saying that it was found that a maximum of 4 or 5 Clo units was all a man could be given and remain mobile and dexterous enough for his military task. The fact had to be faced that we might calculate the insulation required for an indefinite comfort and efficiency, but in very many cases could not supply it. It might suffice for a short time of exposure only. What was needed was a scientific measure of inadequacy of the best possible clothing, as well as one of theoretical and unattainable adequacy. This measure was supplied by the introduction of the *Tolerance Time*, by Doctor Talbot and the Climatic Laboratory of the O. Q. M. G. (fig 7). There is a severe physical limitation on the maximum insulation obtainable in gloves or mitts, pointed out by Van Dilla. 1½ to 2 Clo units is all that is theoretically possible due to a physical effect of the small radius of curvature involved. While the Clo determination is of the greatest use in development work on clothing, the *Tolerance Time* is the important information for military planning. It is based on a logical and practical definition of the end point of tolerance.

in terms of interference with the particular mission undertaken. The Armoured Corps Medical Lab under Colonel Hatch, has further developed its usefulness, by correlating it with the thermal insulation in Clo units, and mathematical analysis of cooling curves. An investigation of why the incidence of trench-foot in France was much higher in one Division than in a neighbouring Division revealed that the reason lay almost entirely in the neglect of the limitations of Tolerance Time, and that men were not being relieved at short enough intervals.

The inadequacy of the best thermal insulation we could provide also turned our thoughts to the use of auxiliary heating, in *electrically heated clothing*. A great deal of work was done in Canada and later at Wright Field and at Pensacola. A fact of physiological interest emerged. Everybody knows that it is the hands and feet that first feel cold. Quite naturally then the earliest suits supplied all or most of the heat to the extremities. Yet it was found that unless the heat were distributed in a proper proportion over the body, giving less than 10% of the total to each hand or foot, it was impossible to maintain a man in comfort for more than an hour or two, however much total heat was supplied. If there is too much heat to the extremities, the skin is warm and temporary comfort ensues. But the resulting vasodilation encourages a steady drop of deep body temperature, and eventually this falls low enough to bring on acute discomfort. We have had subjects, in electrically heated suits with improper distribution, eventually shivering (from low deep body temperature) and sweating (from hot extremities) at the same time. New evidence of the dual control, peripheral and central, of temperature regulation has been provided. A great deal of work has now established the proper distribution over the body and over specific parts of it, such as the hands, and charts are available through the cooperation of the General Electric Company by which the total electrical energy required in any circumstances can be ascertained. A simple device for the automatic regulation of the amount of heat supplied in accordance with the requirements has been developed and adopted by the R C A F but not elsewhere. There has also been an air-heated suit developed, (by Canadian and by British workers), but it turns out that the same construction is more suitable for use as an air-cooled suit, to maintain men in efficiency in intolerably hot environments.

One most important phase of the activities of physiologists has been that they have left their laboratories, even their hot or cold chambers, to study the problems in the field. Figure 8 shows just one example to illustrate this. It is of a U S expedition, on which we had several Canadian

observers, to Mount McKinley in Alaska to study clothing and equipment. Only by experiencing themselves the actual conditions for which they were to find suitable clothing could physiologists produce practical results. A development of great permanent value was the growth of *field testing*, under the Quarter Master Board, the O Q M G, and the N R C. Co-ordinating Committee in Canada where the final products of research were put to the crucial test by being used by troops in conditions closely similar to those for which the items were designed. It was realized that unless such field tests are made by statistical design and the results evaluated statistically, they can lead to false conclusions. A new science of field testing has been developed which calls for the application of not only physiology but of G. I. psychology of statistics and of common sense. It is to be hoped that this new science will find further application in the peace time problems of the consumer.



Fig 8

Parallel to all this research of Biophysical nature, purely physical investigations of the nature of the thermal insulation provided by fabrics were proceeding, chiefly under Doctor Larose at the N R C Laboratories, Canada, Doctors Harris and Fournet at the U S Bureau of Standards, and at Listers Ltd, in England. The results can be summarized in a very important generalization. The thermal insulation of an empty air space increases with its thickness but soon reaches a maximal value (after the thickness exceeds $\frac{1}{2}$ ") because of the natural convection currents set up. If, however, the space is filled in with textile fibres, which prevent the convection currents, the insulation continues to be proportional to the thickness up to any thickness that may be tested. Moreover, as long as the bulk density of the filling material be low, the insulation is the same whether the filler be wool, cotton, kapok or whatever else. Thus for materials of low bulk density, it can be said that the thermal insulation of a fabric is simply that of the thickness of still air entrapped. About 4 Clo units per inch thickness is obtainable. Figure 9 is from a class

ical piece of work by Doctor Iarose (The same fabric was used throughout the thickness being altered by different degrees of compression) The realization of this fact was of the greatest importance It prevented us from wasting time on a wild goose chase to find some new material that would have a unique insulation for a given thickness, and it turned our attention to the ways in which clothing *could* be improved Fabrics should be chosen, or developed, to have the best resistance to compression so as to maintain thickness and thermal insulation under service loads, moisture and wear, and yet have the best flex-

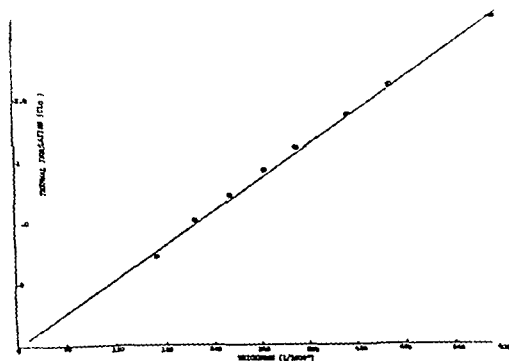


Fig 9 Thermal insulation of double pile fabric (wool) variation with thickness



Fig 10

ibility, durability and light weight If it was found that a double pile fabric (with the ground fabric between two pile faces) stood compression better than a single pile and this has been widely adopted Clothing could be designed so that reduction of thickness at elbows, knees etc was avoided Figure 10 shows the R C A F Type E flying glove developed by Kitching and Pagé, also adopted enthusiastically by the U S Air Transport Command The fourchettes of the fingers are curved to the position in which the hand will be 90° of the time There is a great gain in warmth and manipulative freedom In this way a very considerable improvement in military clothing was effected even if the garments would not please conventional tailors

I can touch only very briefly on the question of

moisture in clothing Men of experience in the North such as the R C M P and explorers, all agree that the accumulation of moisture, from the body rather than from outside, is the greatest hazard If the outer garments do not permit the passage of water vapour, and men are working, the moisture from sweat will condense in the outer layers and the thermal insulation will be lost Impermeable fabrics, such as the plastic coated fabrics developed during the war, may serve well to shed rain, but men cannot live and do physical work continuously, especially in cold-wet conditions, in impermeable garments The exclusion of moisture from without which could otherwise be continuously evaporated by the body heat, has been at the cost of permanent retention of moisture from the body in the clothing It has been a battle, not yet won, to convince the military authorities and even some scientists, of this It is water repellent, rather than waterproof, fabrics that are required in these circumstances Where exclusion of outside water is essential, Bazett and Siple have suggested that we provide a second impermeable layer very close to the skin Here the accumulation of moisture will soon retard further evaporation and the layer of insulation between this inner vapour barrier and the outer barrier (say a rubber boot) will retain its dryness and thermal insulation

The whole subject of humidity in clothing has been elucidated by the work of Goodings and Kitching in Canada and Fourt in the U S The resistance to transfer of water vapour of a given fabric can be defined in a manner exactly analogous to the thermal insulation The unit is the cm of "dead" air (i.e. completely still air as in a very narrow air space)

Resistance to transfer of water vapour

$$= \frac{\text{Difference of Vapour Pressure}}{\text{Flow of vapour per unit area}}$$

Total resistance (clothing plus air)

$$= \frac{P_{\text{Skin}} - P_{\text{Air}}}{\text{gms/SqM/Hr}}$$

$$\text{Cms of dead air} = 8.5 \times \frac{\text{mm Hg}}{\text{gm/SqM/Hr}}$$

Heat loss by evaporation from body

$$= \frac{5 (P_{\text{Skin}} - P_{\text{Air}})}{\text{Resistance in Cms}} \text{ Cals SqM/Hr}$$

Doctor Goodings devised relatively simple methods by which the resistance could be measured on a sample of fabric Physiological knowledge enables us to state how many "cms of dead air" resistance is consistent with comfort in

given circumstances. A startling result of this work is the generalization that the permeability of a fabric to water vapour bears very little relation to its porosity to air. The vapour moves through the fibres, even if there are very few holes. A tightly woven, but thin fabric, will have as low or a lower vapour resistance as a thicker more open fabric. This has had a great bearing on tropical clothing, in which we need the least possible resistance to evaporation, which, in hot conditions, is the all important mode of heat loss. Theory based on the laboratory work predicted that a thin tightly woven fabric would be cooler than the conventional, open weave, but thicker fabrics. Dill verified this by observation and field tests in the South Pacific. Intensive work on the humidity within clothing was done by Kitching and myself in the later years, in Canada, and by Forbes and Belding and others in the Harvard Fatigue Laboratory. Results cannot be discussed here.

From the consideration of humidity and moisture in clothing it is an easy step to consider clothing filled with water, as in immersion in the ocean. Not only the insulation of the clothing is lost but also the insulation of the outside air, and exposure of less than an hour even in water at 60°F proved fatal. *The only way in which survivors of ditching or shipwreck can be protected is to ensure that water does not enter their clothing.* If this is done, men can, and have, survived many days of immersion even in the North Atlantic. Although an "exposure suit" to do this had long been in use in the Norwegian Mercantile Marine and had saved many lives, and although Dr L. Irving spent all his powers of persuasion and energy in advocating such protection as early as 1939 and 1940, it has been a very hard task to convince the Naval authorities. They continued to stock life-rafts with rations for several days and to ignore the fact that if clothing were wet men would not survive to eat them. To evaporate only five pounds of water from clothing by body heat requires more than 1300 cals, a very generous emergency ratio for one day. Eventually the dogged persistence of Dr Newburgh and others in pointing this out, and the work of Pask in England, was rewarded, but almost too late to save many lives in this war, though in the R A F, R C A F and Royal Canadian Navy such exposure suits have repaid all the work of the physiologists. Figure 11 shows one such exposure suit. It weighs only a few pounds, can be donned over clothing in less than a minute, and provides adequate flotation. It is suggested that it would be a very desirable safety measure if all passenger liners carried such suits for passengers and crew.

Due to the work of Newburgh and Bartell and of Kitching and Goodings (working with the R A F), we now know two different ways in

which it is actually possible to make an exposure suit which will not allow water to penetrate to the clothing on immersion, yet have so low a resistance to water vapour (less than 5 cms of dead air) that it can be worn continuously even in warm surroundings without discomfort. Such a suit solves the problem of a pilot, who on ditching of the aircraft may not have time to don one of the suits already described.



Fig 11

The work of prevention of immersion foot and trench foot, notably by Spielman, followed the same lines of attack. I can only refer you to the intensely interesting work of the Germans on the subject of the effects of exposure to water, described in the C I O S reports of the brilliant investigation of Major Leo Alexander. My own finding in investigation of enemy science was that, in general, the Germans had neglected protective clothing almost completely, and their failure to put physiologists to work played a large part in their defeat in winter campaigns against Russia.

I have left no time to discuss at all the problems

of heat exchange in hot conditions, and the outstanding work of Robinson, of the Climatic Research Laboratory, and of others in this field. This has been deliberate on my part. I had to choose whether to discuss, inadequately, one phase of the subject or to discuss both phases, very inadequately indeed.

It is my opinion that physiology has made a considerable contribution to wartime problems in the field of protective clothing, but wartime conditions have made an even greater contribution to

physiology. We have learned new facts of physiology, we have been forced to tackle problems of great practical importance to peacetime as well as wartime living, and to agree on units and methods of measurement, we have left our laboratories and learned by actual experience how we can apply our science, and we have the new science of field testing. It is to be hoped that we will not now surrender these gains and retire completely to our ivory towers, but will continue to apply our physiology to the problems of peace.

PROBLEMS OF VISUAL PHYSIOLOGY DURING THE WAR

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The importance of vision in all kinds of military operations makes it inevitable that in time of war a great deal of attention should be directed toward the investigation of visual problems. The extent and diversity of this work during the past war make it impossible to cover the entire effort in a short review, even if one person could possibly be familiar with all its phases. For this reason a few examples have been selected, to show the character of some of the investigations that are of particular interest to physiologists.

The examples selected are all concerned with night vision. Night vision, which concerns us very little in ordinary life, becomes suddenly of vital importance in war time, when artificial lights dare not be used freely, and both sides take advantage of the cover of darkness.

One of the first problems considered was that of the selection of personnel on the basis of their sensitivity to light, after complete dark adaptation. The relation between vitamin A and night blindness was understood, and survey tests by Hecht (Fort Bragg), Lohencrantz (USS Enterprise), and McDonald (Randolph Field) showed a wide distribution in sensitivity to light in the military population. Hecht drew attention to the greater incidence of poor night vision among enlisted personnel as compared to officers, which might well be related to a less satisfactory nutritional history. The promise of the usefulness of selection was not borne out. This was the result of the inherent difficulties of making reliable tests on large numbers of individuals in a limited period of time. "Mass testing" was not reliable, individual testing was too time consuming and required skilled operators. The Canadians were able to utilize individual testing, and our Navy ultimately adopted individual testing procedures. On the whole, however, little use was made of testing

although the effort probably had some value in bringing about an awareness of the possibility that some individuals could be dangerously lacking in ability to see at night.

The detailed reasons for the difficulties encountered in night vision testing are of interest to physiologists. In the first place, vision at threshold is uncertain, the "threshold" is not a sharply defined magnitude of visual stimulus, but rather a range of magnitudes over which the probability of seeing varies from zero to certainty. There are various possible ways of determining the threshold to light reliably, they all entail repeated observations and patient, cooperative subjects. This is not entirely a matter of "human variability," indeed with trained subjects this scarcely enters the picture at all over the moderately short interval of time necessary to make a fairly extended series of observations. The main reason for the uncertainty of seeing at the threshold is purely physical. Hecht, Schlaer and Pirenne (*J. Gen. Physiol.* 25: 819) in 1942 drew attention to the fact that the absolute threshold of vision entails the action on the retina of a very small number of quanta of light, and that as a consequence the statistical fluctuations in the flow of light quanta from an object at the threshold of visibility will cause uncertain seeing over a considerable range of intensities. These uncontrollable physical fluctuations of the energy content of a "constant" light are sufficient to account for the observed uncertainty of seeing. Apart from its interpretation, the recognition of the statistical nature of the visual threshold was important in the practical solution of many visual problems.

In addition to this, the observer himself does exhibit variability when tested repeatedly at intervals of a day or more. The source of this is unknown, it means that reliable measurement of

an individual's ability to see at night must involve several tests covering a period of a few days. Rough screening tests, therefore, are useful only if the standard is set so high that a large proportion of individuals are rejected, or if a large proportion of "doubtful" cases are called back for one or more re-tests. The waste and nuisance of these requirements more than offset the possible value of the selection.

Another factor that impeded the adoption of selection methods was an inability of those concerned with establishing the tests to agree on the nature of the test. Physiologists were inclined to the view that a simple test of threshold to a flash of light, viewed in the peripheral retina, was sufficient to indicate whether there was any basic deficiency in night vision. Those in the military services preferred a test more plainly related to practical seeing at night, such as ability to recognize form at low brightness levels. No clear-cut guiding principle could be applied, and while disagreement was compromised readily enough, the fact that such an apparently trivial issue could be raised and not be resolved by appeal to scientific principles could not fail to decrease confidence in the value of night vision testing. Subsequent experiments have shown that most properties of vision at low illuminations are strongly correlated. Thus C. J. Warden, demonstrated a very high correlation between the threshold to a flash of light and the ability to detect motion in the visual field at low illuminations. Form recognition is well correlated with light perception at very low brightness levels, but at higher levels, still within the range of rod function it weakens noticeably, although remaining moderately high. Cone function was known, from the results of Hecht's and McDonald's surveys, to be only very weakly correlated with rod sensitivity. On bright nights the level of illumination is high enough to permit an important contribution from cone vision, so it is clear that a simple light perception test could fail to reveal important deficiencies in vision under conditions that are important in military operations. On the other hand, rod vision is still extremely important even when foveal vision can function for specific tasks, and it would be a mistake to fail to measure the essential night visual mechanism in a purported test of night vision! The absence of guiding principles in these considerations is painfully evident, and the war did not foster the kind of research in visual physiology that discovers guiding principles.

In connection with the study of night vision testing, and the factors influencing the visual threshold, it is interesting that no dietary or pharmacological methods were discovered for improving night vision in the average population. Massive doses of vitamin A given to an already

adequately nourished group has no effect upon the visual threshold or the rate of dark adaptation. Occasional reports were received of the beneficial effects of drugs on night vision. None of these was substantiated. Since only a few quanta are required for seeing, it is evident that no very large factor of improvement could be expected. Even within the limits of possibility, however, there is no reliable evidence of any methods that produce a significant lowering of the threshold to light or increase in the speed of dark adaptation in trained observers.

Early in the investigation of the military problems of night vision it became apparent that while selection was of dubious value, training in night vision offered great promise. The properties of the night visual mechanism require different habits of seeing from daytime vision, few people have occasion to develop skill in seeing in surroundings that are not well lighted. Training may, therefore, be expected to increase the effectiveness of personnel in night operations. In this field the physiological principles are well established, the dual nature of retinal structure and function is well understood, and the peculiarities of scotopic vision have received intensive study.

The Submarine Service of our Navy pioneered in the development of procedures for night vision training. Here the value of night vision was very keenly appreciated, and an excellent course of practical night vision training, based on sound physiological principles, was part of the preparation of personnel in this branch of the Navy.

The Canadians were among the first to recognize the importance of training in night vision, and when the Air Surgeon, General David Grant, requested the cooperation of the Subcommittee on Visual Problems in developing a program of night visual training for the AAF, we found many suitable methods already perfected by the RCAF, under Dr. Evelyn. Evelyn's night vision trainer was adopted, in principle, with minor modifications to suit the somewhat different and more diverse requirements of the AAF. To take charge of the program of night vision training in the AAF we were fortunate in having in the Aviation Physiologists a group of highly trained and able men organized for just such purposes. The story of physiology in the past war would be far from complete without detailed reference to the activity of these colleagues of ours who joined the AAF and did an important job under conditions that were often arduous and discouraging. It was their responsibility to see that flying personnel were properly instructed in matters pertaining to human physiology under conditions of flight. The subject of night vision training, therefore, came within the province of the Aviation Physiologists. They were well qualified to undertake it, and they carried it

through with their customary effectiveness To prepare them for this work, a group of Aviation Physiologists were given a brief "refresher course" in the principles of visual physiology and some of their applications to the problems of seeing at night This was conducted by the members of the National Research Council Subcommittee on Visual Problems, and by personnel from the Office of the Air Surgeon From this as a beginning, the Aviation Physiologists quickly developed instructional methods suited to their special needs in the particular groups to which they were assigned In the last few months of the war large numbers of Air Forces Personnel were being trained in night vision

The importance of night vision drew attention to many very practical problems of protecting the night visual capacities of personnel Among these is the problem of the illumination of vehicles, ships, and aircraft for operation at night Illumination of vital instruments and controls, of maps, etc., is frequently necessary, any such illumination cannot help but impair to some extent the night vision of those who must use it Dark adaptation is likely to be "spoiled," glare effects and unwanted reflections in windshields, etc., make it more difficult to see faint objects in the darkness, outside In addition, escaping stray light may turn the vehicle or ship into a "sitting duck" for the enemy These effects can be very greatly reduced by careful engineering of the lighting system—not that this is always done, unfortunately Still further protection is possible by the application of a well-known principle of classical visual physiology, the principle underlying the well-known "Purkinje phenomenon" According to this, the maximum spectral sensitivity of the retinal cones lies farther toward the red end of the spectrum than that of the rods Illumination is usually required in order to make possible seeing that requires high visual acuity, that is, cone vision Any degree of illumination that permits the cones to function will necessarily stimulate and affect the dark adaptation of the retinal rods, which are more sensitive than the cones to light of any color However, by the use of red light, this unwanted action in the rod mechanism may be minimized In the red end of the spectrum, the rod threshold is nearly equal to, or only slightly less than, the cone threshold, while in any other part of the spectrum it is many times lower Of two types of illumination, one red, the second any other color of predominantly shorter wave length, so adjusted to give equal brightness and hence equal acuity as measured by the cone mechanism, the red lighting will appear "darker" to the rod mechanism, and hence will be less disturbing to night vision (cf Hecht and Yun Hsin, *J Opt Soc Am* 35 261, 1945) Purkinje's original observation of this effect

was made more than a century ago (*F zur Physiol d Sinne* 2 109, 1825) and its explanation in terms of the absorption spectra of the photosensitive substances in the two types of retinal receptors is common knowledge in physiology Consequently when Professor A V Hill in 1940 called our attention to the military and naval problems of illumination, the fundamental principle to be applied was obvious to us, as it was, of course, to him It required only the demonstration that the advantages to be gained by the use of red illumination in practice were real, and that no unforeseen complications arose This we, and numerous others independently, were able to do for many applications In Canada, Solandt and Best (*Canad Med Assoc J* 49 171, 1943) demonstrated the application to the Canadian Services, and the lead taken by them had much to do, I believe, with the adoption of red lighting in our own Services

Our Navy was particularly progressive in the use of red lighting in their ships and aircraft, and utilized its advantages through most of the war Red illumination in the interior of ships permitted personnel enough light to move about comfortably and see with the necessary acuity, with comparatively slight loss in dark adaptation so that upon going out upon unlighted decks only a very few minutes would be required to achieve full night visual sensitivity The employment of red "dark adaptation" goggles in the development of which Dr Walter Miles played a large part, accomplished a similar purpose in a wide variety of applications (Federation Proc 2 1943) Red instrument illumination was employed in Navy night fighter airplanes to provide the easiest possible instrument visibility with the least possible disturbance to night vision, either by glare or by loss of adaptation caused by scanning the instrument panel Our armored forces, it is my understanding, likewise availed themselves of the advantages of red illumination for lighting the interiors and instrument panels of tanks

The military use of red illumination to protect night vision was a direct contribution from visual physiology Here the guiding principle was clear, well-established and well understood Recommendations could be made with confidence, and applications were straight forward in many cases and ultimately proved their value in practice

In another example of a practical visual problem quite the opposite was experienced This problem concerned the effect of vibration upon the visibility through optical instruments Without going into details, it may be said that while vibration could be measured, and its effect on the optical image in an instrument computed, there was little gained from this, for there was no rational procedure for estimating the effect it would have on visibility Something is known of the laws govern-

ing spatial summation of excitatory effects from different retinal elements that would be stimulated by the erratically moving image, something is known of the temporal summation of excitatory effects initiated at different times. Little, however, is known of the relation between them, and this knowledge was required for a scientific approach to the problem of vibration in optical instruments. Until it is possible to state the principles governing the summation of the excitatory effects from one group of retinal elements, stimulated at a particular instant, with the excitatory effects of another group nearby, stimulated at some later instant as the vibrating image sweeps over them, it will not be possible to give a satisfactory solution to the problem of visibility of a vibrating image. Various plausible assumptions based on known principles could be made, and were moderately successful in furnishing approximate answers, but visual physiology failed to provide a guiding principle and because of this a satisfactory

solution of the practical problem was not possible.

These examples give a fairly accurate cross section of the successes and failures of visual physiology applied during the war to practical problems of seeing. Where there was sound understanding, well established principles could be invoked and useful applications made with a minimum of lost effort. Such was the case with the principles of scotopic vision, as applied to night vision training, and with the "Purkinje phenomenon," applied to the use of red illumination to protect night vision. Where knowledge of fundamental principles was indistinct or lacking, there was disagreement and hesitation in coming to applications of practical value, and the empirical knowledge hastily acquired to answer specific practical problems was a poor substitute for genuine understanding. War conditions did not foster the development of the truly scientific aspects of visual physiology, in this respect there has been little progress in the last five years.

PHYSIOLOGICAL CONTRIBUTIONS TO THE PROBLEM OF SHOCK

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The physiological contributions made during World War II to the problems of shock have had a notably cleansing effect on our concepts of this syndrome. It is as though the investigations finally broke away from the restraining influence of too many theories—some of which had gained a large following, and a fresh start made to verify, extend and evaluate the pertinent facts without bias.

You will recall that in this country, investigations of shock received their main impetus during World War I, and continued with considerable momentum between the wars. The literature on the subject grew to fairly staggering proportions and at the onset of World War II, much of it was in a highly controversial state (1). I recall the dismay which two of my colleagues and I experienced in 1941, when we made a search of the literature for definitive measurements of bodily changes in human cases of shock. Reliable facts were scarce and disconnected. By contrast we are now in possession of a wealth of information that has been gleaned from several clinical studies carried on during the war. Although a great deal had been done by 1941 in the way of experimental studies on animals (2, 3), most of these investigations had been directed toward proving or disproving the current theories. Generally speaking, this is an effective way of advancing knowledge, provided

one does not commit the error of assuming that one explanation necessarily excludes others. Perhaps the most significant change in our attitude during the past four to five years has been the recognition that shock may have several causes and that their relative importance in any particular instance depends upon the nature of the injury.

There is no doubt that the war-time researches on shock and its treatment, especially the development of methods for storing whole blood, the preparation of plasma, and the exploration for new blood substitutes, have achieved practical results of inestimable value. In my opinion, there has been another perhaps less obvious gain which may eventually have far greater significance. That is, that shock can be used as a tool for investigating the effects of tissue hypoxia which, after all, is a fundamental common denominator in many forms of disease. Experimental shock presents opportunities for creating progressive metabolic disturbances of any degree of severity and for examining their effects on intermediary metabolism and on functional changes of the capillaries, kidney, liver, etc.

In surveying what has been accomplished during the past few years, one may observe several trends. For one thing it is obvious that a number of new tools and techniques, mainly developed during

peacetime, have been applied to the problem of shock with telling effect. These include the direct Fick method of measuring cardiac output in man, improved techniques for estimating blood volume, optical registration of arterial and venous pressures, renal clearance methods, the use of isotopes, and a host of chemical methods for analyzing the body fluids and tissues. These new tools have given us a more complete and accurate picture of the bodily changes in shock with the result that we are in a much better position to evaluate certain concepts regarding the cause of shock.

Without question, one of the most important steps that was taken during this war to advance our knowledge of shock was the initiation of comprehensive studies of civilian accident cases (4). In due course I hope we shall also have full reports of the observations that were made on the battle fronts. Much valuable and fundamental information has been gained from these investigations of the physiological changes resulting from various types of injury in man, and they have given us valuable confirmation of the results of animal experiments.

We have also seen strides in the character and quality of the experimental studies. I refer here to the efforts that have been made not only to demonstrate that shock as seen in man can be reproduced in animals, but also to standardize the methods. Both are extremely important. The frame of reference for an investigation of the bodily changes associated with a clinical syndrome must be the signs and symptoms by which the syndrome is defined clinically. Since most investigations of experimental shock have required the use of deep anesthesia, we often meet with great difficulty in determining the relation of the experimental findings to the problem in hand. Anesthesia is a serious complication. It not only modifies or masks entirely the signs which constitute the proof of the presence of shock, but it also alters the physiological response to the injury. Wiggers (3) has expressed the view that a uniform anesthesia has the advantage that it eliminates the visual, auditory and psychic factors which complicate the study. I would remind you however, that these may be part of the factors involved in the response of the organism to injury. Furthermore, it is erroneous to assume that the establishment of a uniform degree of anesthesia before injury guarantees that it remains constant after injury. It is well known that the tolerance to anesthetics and to a variety of toxic agents decreases markedly as shock develops. A partial solution of the difficulty has been achieved by selecting traumatic procedures (e.g. muscle contusion) with which the use of anesthesia can be limited to the period of injury. One may then observe the subsequent development of the signs of shock without interference of

the anesthetic. In this manner it has been possible to reproduce consistently in dogs the classical signs of shock observable in human cases (5) (e.g., thirst, cold extremities, various signs of peripheral constriction and reduced blood flow, fall in body temperature, central and nervous depression and finally coma). In my opinion, the clinical signs warrant more attention in experimental studies than they are usually accorded, and I am sure that they will be given greater attention as we become more adroit in devising experimental procedures that do not require the use of general anesthetics. I have encountered several papers in which the investigators claimed that the animals were unanesthetized, only to find that repeated doses of morphine were employed. Morphine, even in small doses, has very considerable effects on the circulation and its influence on shock is certainly not well understood. On the basis of practical experience, medical officers during the war sounded a warning against its routine use in shock.

The groups that assembled under the National Research Council at the beginning of the war to consider ways and means of accelerating the investigation of shock were keenly aware of the dire need for standardizing the methods for producing shock. In 1942, Wiggers stated that "the effort to devise a standard procedure that unfailingly produces shock seems as hopeless today as it was in 1903" (3). Since then notable progress has been made. Most recent investigators who have employed some form of traumatic procedure have made very considerable efforts to control the severity of the injury and to correlate it with mortality rates and survival times. They have also tried to define their methods in sufficient detail to enable others to confirm their findings. Yet I do not believe anyone would be willing to claim that the procedures unfailingly produce shock in every instance. In order to make this claim, the severity of injury would of course have to be adjusted to individual variations in the resistance to trauma. In so far as I am aware, the nearest approach to the ideal has been achieved with hemorrhagic shock in dogs by a rather simple procedure devised by my colleague Doctor Walcott (6). A large cannula is inserted in the femoral artery under local anesthesia and the dog "bled out" in the space of a few minutes. One-quarter of the blood that has been collected is then immediately returned to the circulation. Under the experimental conditions defined by Walcott, the animals consistently succumbed in shock in about four hours. The predictability of the results, the simplicity of the procedure, and the fact that no general anesthesia is required, has made this method a highly useful tool for the investigation of hemorrhagic shock in dogs, as well as for the precise comparison of various therapeutic procedures.

The number of methods that have been employed to produce shock experimentally has steadily increased. To some extent they represent attempts to duplicate the types of injury encountered in civilian and military practice. Even if they only partly satisfy this condition, they deserve careful study in order to extend our knowledge of the variety of events which may lead to shock. The differences in response to various types of injury must eventually form the basis of a more refined therapy. The traumatic procedures which have been employed during the past few years include, tourniquet, crush, compression, contusion, femoral vein ligation, gun-shot wounds, various forms of intestinal trauma, freezing, burns, "gravity shock" and nerve stimulation. A large variety of toxic agents have also been employed. It seems to me that the value of the studies of such different forms of shock could be greatly enhanced by more general use of measurements of cardiac output, blood volume and arterial CO_2 , by which one can at least make a fairly objective comparison of the degree of circulatory failure and metabolic disturbance.

There is time here to consider only a few of the recent findings. The general results which I shall present are concerned mainly with experiments on trauma and hemorrhage, carried out by the group in my laboratory (5). I have also drawn on the results of the studies of clinical shock organized at Bellevue Hospital in New York by Dr. Dickinson Richards, a cooperative venture involving several groups of investigators (7).

The procedure which we have employed in producing traumatic shock in dogs (8) is essentially the one described by Solandt and Best (9). Under surgical ether anesthesia, both hind legs were contused with a light raw hide mallet. The blows were distributed over the muscular portions of the extremity to avoid injury to bones, large blood vessels and nerves. Soon after coming out of anesthesia, the animals begin to show the classical signs of shock. The heart rate climbs gradually, reaching 240 to 250 per minute in the later stages of shock. The end is invariably announced by a more or less sudden slowing of the beats. The blood pressure was not found to be a trustworthy criterion of the severity of shock. To be sure the pressure sooner or later falls to low levels, but this may happen late as well as early. For instance, some animals maintained a mean pressure of 90 to 100 mm Hg (control 100 to 120), for several hours after the injury, and then suddenly died. One dog in which the mean pressure stayed at 60 mm Hg for five to six hours after trauma recovered without treatment. After simple hemorrhage, the blood pressure may continue well below this value for extended periods, and the animal have an uneventful recovery. Furthermore, my colleague Dr. Deyrup,

has observed that dogs in which the mean blood pressure was reduced to 30 mm Hg by histamine injection (10), were able to walk around the laboratory without apparent difficulty. Therefore at least in the dog, blood pressure by itself is not a dependable index of the severity of shock.

The hematocrit values and to a lesser degree, the plasma protein levels are usually higher immediately after trauma than during the control period before etherization. These changes arise from constriction of the spleen and from the small reduction in plasma volume caused by ether. In the trauma experiments on splenectomized dogs, the hematocrit value either remains unchanged or falls slightly. Another feature of the hematocrit and the plasma protein values which at once strikes the eye is that they remain essentially unchanged during the post-traumatic period regardless of whether the animal develops shock and succumbs after several hours or fails to develop signs of shock and recovers. These observations were important to us four years ago (5) for they revealed that shock could be produced experimentally by trauma without evidence of progressive hemoconcentration.

Blood volume determinations (dye method) in the same series of experiments showed a) that the dogs that developed shock and died had suffered a loss of 30 to 40 per cent in blood volume, b) that this reduction occurred at time of injury, and, c) that the progressive nature of shock was not related to a gradual decrease in plasma volume (as postulated by the theory of generalized capillary leakage) because the volume remained practically unchanged after trauma until the animal died.

Although there has been widespread skepticism regarding the validity of blood volume measurements especially in shock-like states, recent evidence has, I believe, answered the most serious questions. One source of difficulty is that in shock the circulation in superficial veins is notoriously poor. Therefore, in order to obtain fair samples of the circulating blood, these must be drawn from deeper vessels preferably from an artery, otherwise the dye method or any method will give erroneous values. Intravascular hemolysis, which frequently occurs in traumatic experiments on dogs, does not invalidate the plasma dye determination provided no additional hemolysis is permitted when the samples are drawn. It has been postulated by some workers that a large fraction of the dye is lost very rapidly after the injection. I think this is unlikely in as much as simultaneous determinations of plasma volume with dye and with such entirely different test substances as bovine albumin, bovine globulin, and the polysaccharide SIII yield identical values (11).

A considerable amount of evidence indicates

that there is an unequal distribution of erythrocytes in the circulation (12, 13 and others). According to this, the "body hematocrit" is considerably lower than the central arterial or venous hematocrit and therefore the total blood volume calculated from the plasma volume and from the hematocrit value would be too large. This conclusion received support from earlier tests with the carbon monoxide method (14) and more recent ones with the radioactive iron method (15).

More precise techniques for determining carbon monoxide and other refinements in the CO method developed recently (16, 17), disclose that there were technical errors in the procedures employed twenty years ago which account for the low values reported. Furthermore, it is now recognized that the small vessels and capillaries contain a relatively small fraction (15 per cent or less) of all the blood in the circulation. Hence, even if the ratio of cells to plasma in this region of the vascular bed is considerably below the central hematocrit, this would not greatly influence the estimation of total volume. However, more work needs to be done on this problem with the radio iron method before we can definitely decide the exact extent to which unequal distribution of erythrocytes affects the calculation of the total blood volume from dye method.

The examination of the disappearance rate and mixing time of T-1824 in a large series of clinical cases (18) of shock reveals, (a) that changes in the rate at which the dye escapes from the circulation bear little if any relation to the presence of shock but seem to be determined by the nature of the injury, (b) that the mixing time is increased but not indefinitely prolonged. The average disappearance rate of the dye in patients in severe shock from skeletal trauma and hemorrhage was the same as in patients with similar injuries but not in shock. In cases of burns and abdominal injuries with peritonitis however, the disappearance rate was markedly increased, as one might expect from the rapid leakage of plasma which characterizes these conditions. As for the mixing time, the average values were as follows: (a) Normal subjects—9 minutes; (b) Patients in severe shock after hemorrhage or skeletal trauma—15 minutes; (c) Patients with hemorrhage in skeletal trauma but not in shock—7 minutes. From an analysis of all the dye curves we came to the conclusion that in man the probable error in estimating the blood volume from the ten minute sample was ± 2 to 3 per cent.

The progress which has been made in the study of the technical and theoretical aspects of the measurement of blood volume permits one to proceed with somewhat more confidence in evaluating the changes that have been observed in clinical and experimental shock. As noted above, we found

in muscle trauma experiments that the dogs in shock had usually lost 30 to 40 per cent of their blood volume (8). In clinical cases of shock we are at some disadvantage because one cannot compare the results with normal control values in the same patients and must therefore rely on average normal values. Data from several sources indicate that the average normal blood volume in man is around 83 cc per kgm or 3100 cc/sq M. The individual variations are fairly large, but not so in comparison with the changes observed in cases of shock from hemorrhage and skeletal trauma. In patients judged to be in severe shock at the time of admission, the blood volume was with few exceptions below 55 cc per kilogram or 2000 cc per sq M (19). It will be noted that the degree of reduction corresponds with that observed in dogs. Expressed in another way, it means that a man of average size who displays unmistakable signs of severe shock after traumatic injury has lost approximately two liters of blood. We have here direct evidence to support the lesson learned from practical experience early in the war that effective resuscitation of severely wounded men often requires 2 to 3 liters of blood or blood substitute. Another observation which has practical interest was obtained from a correlation of the blood volume reduction with the number of fractures (19). From this it appears that with only few exceptions the cases with fractures of 3 or more extremities or with pelvic fractures have blood volume reductions exceeding 30 per cent.

These observations on blood volume in clinical cases of shock are in accord with those reported by Evans (20) and his associates in Richmond. I think it should be pointed out also that all of the critical work recently done on blood volume changes in both experimental and clinical shock confirms the original studies made nearly 30 years ago on wounded soldiers by Keith and by Robertson and Bock.

In the early years of the war, our Canadian (21) and British colleagues were unable to substantiate the claim that hemoconcentration is a criterion of shock. Also in this country a good deal of evidence has now been accumulated which definitely disproves the hypothesis. In the cases of skeletal trauma observed at Bellevue Hospital, the values for the hematocrit and plasma protein determined at the time of admission revealed a trend in the direction of hemodilution rather than hemoconcentration (19). The same was true in patients with hemorrhage except where there was a history of exposure and dehydration. The only cases in which there was consistent evidence of hemoconcentration were those with burns and abdominal injuries with peritonitis. It is clear therefore that hemoconcentration is not a criterion of shock, but the result of certain types of injuries which involve

damage to large areas of the capillary bed resulting in local selective loss of plasma and retention of red cells. So far as we could make out the reduction in blood volume in skeletal trauma as well as in hemorrhage was caused entirely by the escape of whole blood (19).

Before the war there was relatively little factual information on cardiac output changes in experimental shock and none on shock in man. Advance in this direction has contributed greatly to our understanding of the mechanism of shock especially because the cardiac output changes have been correlated with several other measurable alterations in the circulation and with disturbances in the respiration and metabolism.

In the animal experiments referred to above (8) it was noted that the blood volume remained unchanged during the post traumatic period. What then is responsible for the progressive failure of the circulation? Repeated determinations with the direct Fick method (5, 22) reveal a steady decline in the cardiac output, sometimes to only 10 per cent of the normal control value. In the mean time, the oxygen consumption gradually falls to less than half the normal value and the arterial-venous oxygen difference increases until in the terminal stages it approaches the oxygen capacity of the blood. It should also be noted that in dogs the total peripheral resistance calculated from the cardiac output and the mean blood pressure is very much increased (3 to 5 fold).

Thanks to Richards, Cournand and their collaborators who have successfully applied the direct Fick method to man, there is now available a considerable amount of evidence on the changes in cardiac output in clinical cases of shock (4, 7). In severe shock, the cardiac output may be reduced to less than 50 per cent of the average normal value while the A-V oxygen difference is greatly increased, but the dramatic reduction in oxygen consumption recorded in animal experiments has not been observed in man. The over-all peripheral resistance changes reveal another difference. In cases of shock from skeletal trauma the peripheral resistance was, contrary to expectation, either normal or lower than normal. This is surprising in view of the marked signs of widespread peripheral vasoconstriction and the drastic reduction in blood flow in at least one interval organ, the kidney, as revealed by the renal clearance studies (23). In cases of hemorrhage, however, the overall peripheral resistance was somewhat increased above normal. For reasons which are not altogether clear it was markedly high in the burn cases even before hemoconcentration had developed. In patients with low cardiac output and small stroke volume after skeletal trauma or hemorrhage, the right auricular pressure was always greatly reduced, often to values below at-

mospheric pressure. This definitely settles an important point upon which there has been disagreement. Noteworthy changes were observed in the arterial pressure tracings recorded with the Hamilton manometer. The pressure curves were characterized by a sharp systolic rise followed immediately by a sudden drop instead of the gradual fall observed normally in diastole. Hence the mean pressure would be quite close to the diastolic pressure. From correlations of the arterial pressure with other evidences of shock, Richards (7) concluded that "a low arterial pressure when present was a good index of shock, but shock can exist even in an advanced degree with an arterial pressure level that is normal or above normal." It was noted also that there was a far better correlation of total blood volume with cardiac output than with blood pressure.

It is well known that in severe shock the organism is notoriously sensitive to the slightest additional strain on the circulation. Withdrawal of trivial amounts of blood or change in position may precipitate a sudden fall in blood pressure, loss of consciousness and death. Indeed this may occur quite spontaneously or at least without any apparent reason indicating a high degree of instability in the mechanisms that maintain the blood pressure. Barcroft, Edholm, McMichael and Sharpey-Shafer (24) have made a study of posthemorrhagic fainting in human subjects which may explain some of these occurrences. They found that the right auricular pressure and cardiac output often remained unchanged when the blood pressure fell and the subject fainted. In these cases, fainting was related to a two-fold increase in blood flow through muscles (fore-arm blood flow). It was estimated that if vasodilatation of this magnitude occurred generally throughout the musculature, it could account for the observed fall in pressure. Sudden changes in the vasomotor tone may thus be a terminal event in some cases of shock.

It was apparent from the observations made during and following World War I that shock is characterized by severe acidosis. In recent years several investigators have contributed a great deal to this aspect of the problem by a systematic survey of the chemical changes in the blood and tissues. The evidence leaves no doubt that the reduced circulation in shock produces extensive metabolic disturbances (25). In many respects, the changes are similar to those found in strenuous exercise. In both instances, there is a discrepancy between the metabolic demands of the organism and the oxygen supply. In shock, this discrepancy is created by "stagnant anoxia." The pH of arterial blood goes down, sometimes to 7.0 or even 6.9. The lactate, the pyruvate, amino acid nitrogen undergo marked increase. Slight increases in sul-

fate seem to be related to the duration of anuria. The accumulation of these fixed acids and the increase in ventilation reduces the arterial CO_2 to $\frac{1}{2}$ or $\frac{1}{4}$ of its normal value. Special studies have been made of the magnitude and the mechanism of the disturbance in carbohydrate and protein metabolism in relation to the degree of injury and tissue hypoxia (26, 27, 28, and others). From these results it is clear that chemical changes in the blood constitute an objective and quantitative basis for determining the degree or severity of shock, and are therefore extremely useful in any precise investigation of the effectiveness of various therapeutic measures.

Serum sodium and chloride generally remained unchanged. Nevertheless, these electrolytes particularly sodium may, as some investigators claim (29), play a larger rôle in shock than is generally acknowledged. Marked shifts have been noted in the tissue electrolytes (30 and others). Serum magnesium rose from an average of 1.7 to 3.4 m eq/L of H_2O (25). No change was found in the serum potassium until the last hour before death when it began to rise, frequently attaining levels (10 to 15 m eq/L of H_2O) shown to be toxic to the heart (31). The acid-base balance sheets in these experiments (25, 32) showed a slight increase in undetermined fixed acids. The average B-A in the control periods was 11.0 and in shock 14.6. Richards (7) has reported a change of similar magnitude in clinical cases of shock.

Reference has already been made to a good deal of the evidence supporting the earlier work of Blacklock, Phemister and others which indicated that the blood volume reduction in traumatic shock could be explained entirely by local loss of fluid into the injured region. Unfortunately they did not have exact data on blood volume which of course would have clinched their argument. Ashworth, Jester and Lloyd (33) and Nickerson (34) have supplied the decisive facts by showing that the swelling in the traumatized extremities is always equal to or greater than the loss in blood volume. Also in experiments on intestinal strangulation, Evans (35) found the local fluid accounted for the reduction in plasma volume. Furthermore, electrolyte and fluid analyses (5) of blood and tissues in traumatic shock disclose that the local accumulation of fluid in the injured regions is accompanied by a withdrawal of fluid and electrolytes from uninjured tissues. The loss of fluid from the circulation is clearly limited to the region of injury; elsewhere fluid and salts are withdrawn from the tissues to compensate for the loss in blood volume. These findings do not preclude the possibility of generalized capillary leakage occurring in certain forms of shock that are complicated by infection and liberation of bacterial toxins.

The rôle of the nervous factor in shock has been

largely a matter of speculation until quite recently. In animals, Phemister (36) has demonstrated that shock can be produced by prolonged stimulation of the depressor nerves, but it is doubtful if this mechanism has much part in the usual forms of shock. Stimulation of other afferent nerves failed to cause shock unless such stimulation was combined with hemorrhage. Swingle and his associates (37, 38) have reported suggestive evidence that afferent nerves from the region of injury contributed to the fatal outcome, but unfortunately the experiments are not sufficiently well-controlled to make this evidence convincing. So far the best experimental evidence has been obtained from a comparison of the residual blood volume which gives 50 per cent mortality (LH50) in a) simple hemorrhage, b) muscle trauma, c) sublethal hemorrhage plus afferent stimulation, d) and in trauma experiments on dogs in which the afferent nerve to the hind legs had been previously severed. In simple hemorrhage, where the nervous factor is absent, the LH50 is 59.1 cc per kilo. In muscle trauma experiments on normal dogs, it is 73.4 cc per kilo (39, 40). If a sublethal hemorrhage is combined with afferent stimulation (sciatic nerves) the LH50 is 69.0 cc per kilo. When dogs are traumatized after severance of the afferent nerves to the hind legs, the LH50 is reduced to 64.7 cc per kilo as compared with 73.4 in normal dogs. What these results mean is that the afferent impulses from the injured region reduce the ability of the animal to withstand a reduction in blood volume. The clinical picture is also distinctly modified by the presence or absence of afferent impulses. For instance, if a sublethal hemorrhage is combined with afferent stimulation of the sciatic nerves, blood pressure and heart rate records resemble closely those obtained in trauma experiments. If trauma is carried out in dogs with deafferented hind limbs, the general clinical picture and the heart rate and blood pressure records resemble more closely those obtained after simple hemorrhage.

The idea which for many years guided various investigators in a search for a toxic factor in shock was the notion that toxic materials must be liberated from the injured region. So far the efforts in this direction have not been fruitful, but other important clues have been obtained.

Aub and his collaborators (41) investigated the toxicity of fluids collected from muscles which had been injured by prolonged occlusion of the blood supply. The harmful factor was traced to the presence of bacteria (*Clostridia*) which are normally found in dog muscles. It is also possible that bacteria in the gastro intestinal tract may enter the blood stream during prolonged periods of hypotension. In certain types of muscle trauma Prinzmetal (42) and his associates found evidence

that infection could be a large factor in producing shock and death. Likewise the toxic factor in experiments in which shock was produced by intraperitoneal implantation of muscle appears to be of bacterial origin.

The existence of another toxic factor in shock has been demonstrated by studies on the capillary circulation. Chambers, Zweifach and their colleagues (13) found that the early and late stages of shock are characterized by definite changes in the capillary circulation and by alteration in the reactivity of the capillaries to epinephrine. Since these changes can be produced in test animals by blood from dogs in shock, the factors responsible for the phenomena are obviously humoral. Schorr, Zweifach and Furchgott (14) pursued this problem further and have recently presented evidence that early in shock a vasor-excitor material is liberated from the kidneys and that in the later stages of shock the tissue hypoxia gives rise to a vasor-depressor material liberated from the liver and muscles. These investigators have postulated that the vasor-excitor and vasor-depressor principles may be oppositely acting components of a mechanism for regulating the circulation through the capillaries.

While we are considering toxic factors in shock, I would like to suggest a third possibility. Shock produces drastic changes in some of the normal constituents of the blood. At least one of these, CO_2 , is important in the control of the various

body mechanisms and the drop in the arterial CO_2 may itself have deleterious effects on the circulation, central nervous system and on intermediary metabolism.

Many important theoretical and practical aspects of war-time investigations on shock have been omitted from this brief survey. The therapy of shock has of course received a great deal of attention especially the problem of determining the relative effectiveness of blood, plasma, saline and various blood substitutes in restoring blood volume, and in counter-acting the late effects of shock. In hemorrhagic and traumatic shock which constitute the bulk of the clinical cases usually encountered, a large reduction in blood volume is the initial step in the train of events leading to shock and therefore the main emphasis in treatment has consistently been upon early transfusion in adequate amounts. However, one must not disregard the fact that shock can occur in the absence of reduction in blood volume and in that event other measures are required. The cause and treatment of conditions which we at present define as "irreversible shock," simply because the available measures have failed, present an interesting problem, or series of problems that will be solved at least in part by further study of the structural and functional changes in individual organs and tissues. Such information as we have suggests that the causes of irreversibility may well be as varied in nature as the initial disturbances that lead to shock.

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AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS

SYMPOSIUM ON SOME RECENT TRENDS IN NEUROSPORA BIOCHEMISTRY

INTRODUCTION

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In the last few years it has become evident that major contributions will be made to our knowledge of biochemistry through the gathering together of several of the streams of scientific research into a unit that has been called "biochemical genetics" Highly significant investigations, firmly establishing this new branch of science, were begun early in 1941 by Dr George W Beadle and Dr Edward L Tatum in the Department of Biology at Stanford University The organism utilized for these investigations, the red bread mold *Neurospora*, was selected because of its unique suitability for genetic studies, and for its equally satisfactory physiological and biochemical characteristics Indeed the organism was chosen on these grounds,

for the purpose of artificially inducing mutations which would prevent the biosynthesis of specific chemical compounds, and for the purpose of relating such biochemical deficiencies to genetic constitution The results have perhaps exceeded the anticipations

The first paper of this symposium is concerned with a review of the genetic and physiological characteristics of *Neurospora*, the general methods of inducing and isolating mutants and a brief summary of some of the contributions of the program to biochemistry It is the primary purpose of the remaining four papers of the symposium to indicate some of the more recent developments in diverse phases of the work on *Neurospora* The material included in these papers comes, for the most part, from current researches in several different laboratories

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NEUROSPORA AS A BIOCHEMICAL TOOL

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The biochemist makes use of a number of chemical and physical tools in his investigation of metabolic processes. The aim of his investigation is to disentangle the complicated temporally and spatially interrelated biochemical reactions occurring in the functioning integrated cell. The study of cellular reactions and of enzymes, the cellular catalysts facilitating and directing these reactions, has been made possible through the ability of the biochemist to separate individual reactions from the complex in the cell by (a) the isolation and study of pure enzyme systems or (b) the use of chemical poisons or inhibitors which more or less specifically prevent the normal functioning of particular enzymes. As has been pointed out many times, either method of attack leaves something to be desired in the application of the results to the intact cell or organism. The newer, extremely powerful biochemical technique, the use of isotopes, permits a closer insight into the unaltered complex biochemical system of the cell and of the organism, since its application enables the biochemist to trace marked molecules through normally operating cell machinery.

More nearly ideal circumstances for biochemical analysis would be attained if one could reach at will into the cell and alter or inactivate single enzymes, without otherwise affecting the cell or its functioning. Such specific changes are responsible for certain exceptional instances, notably alcaptonuria and other heritable biochemical defects in man and in other organisms. These defects are presumably due to the absence or inactivity of particular enzymes, in alcaptonuria those concerned in certain steps in the oxidation of the aromatic amino acids. The occurrence of these oxidative processes and the functioning of the enzymes concerned in a normal individual could only be recognized on comparison with the metabolism in a defective individual. The study of the inheritance of this and a number of similar biochemical abnormalities has led to the view that they result from changes in single specific genes. More important is the complementary concept that all cellular and organismic potentialities are gene determined—that genes are in dynamic control of every step in cellular metabolism. This approach has led to the hypothesis that genes control the production or specificity of enzymes. (1) If, then, he could reach into the cell and change or inactivate single enzymes by changing or destroying specific genes, the biochemist would have an extremely powerful tool at his disposal to aid in unravelling the biochemistry of the cell.

Although we cannot as yet alter or inactivate particular genes at will, studies with the pink bread mold *Neurospora*, initiated several years ago at Stanford University (2) have proven that gene mutations can be induced in a random fashion in this organism and that some of these gene mutations result in the failure of specific biochemical reactions.

Neurospora was selected for definite reasons. First, it is a biochemically versatile microorganism capable of carrying on the synthesis of its protoplasmic constituents from known substances. Second, it is an organism which can be easily grown in large quantities by purely vegetative means for biochemical study. Finally, and perhaps most important, it is ideal for genetic studies, in contrast to most other fungi and to all bacteria.

Neurospora is an ascomycete, and its life cycle, as worked out primarily by Dodge and by Landgren, makes it exceptionally well suited for biochemical and genetic studies. The fact that it is haploid, containing in each nucleus only a single representative of each of its seven chromosomes and therefore of each gene, permits the immediate detection of the effect of a gene mutation in a strain containing nuclei of only one type. Such genetically homogeneous strains can be readily obtained by the isolation of single ascospores and the propagation of the resulting strains. Since *Neurospora* is heterothallic, crosses can be made, and the inheritance of a desired character followed in the offspring. Classical genetic methods are therefore available for the study of the genetic basis of a character.

In the geneticist's picture of the relation between gene and enzyme is correct, we might predict that any enzymatic reaction could be affected by gene mutation. Nevertheless, certain types of reactions are easier to detect and study in a large number of individual strains. These are reactions the failure of which results in the inability of the organism to synthesize a substance essential for its growth. Such biochemically deficient strains should be readily detected by their inability to grow in a simple medium adequate for the original strain. The failure of such a synthetic reaction, essential for growth in the simple medium, would not be lethal if the missing product could be supplied in an available form in the environment, as can vitamins and amino acids for many organisms, from bacteria to man.

The techniques developed for obtaining and detecting mutants of these types in *Neurospora* involve irradiation, then isolation and cultivation of

haploid strains, and finally testing the strains for growth in a minimal synthetic medium, containing inorganic salts and nitrogen, a carbon source, and

ing perhaps 100 different gene mutations are characterized by deficient synthetic capacities, each strain requiring for growth an exogenous

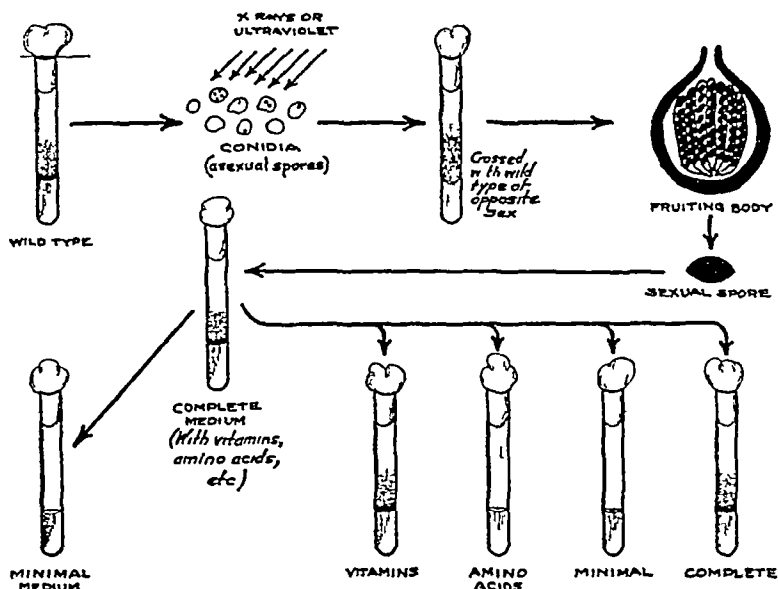


Fig 1 Procedure of producing and detecting biochemical mutant strains in *Neurospora* Reproduced from the American Scientist by permission of the author and of Yale University Press

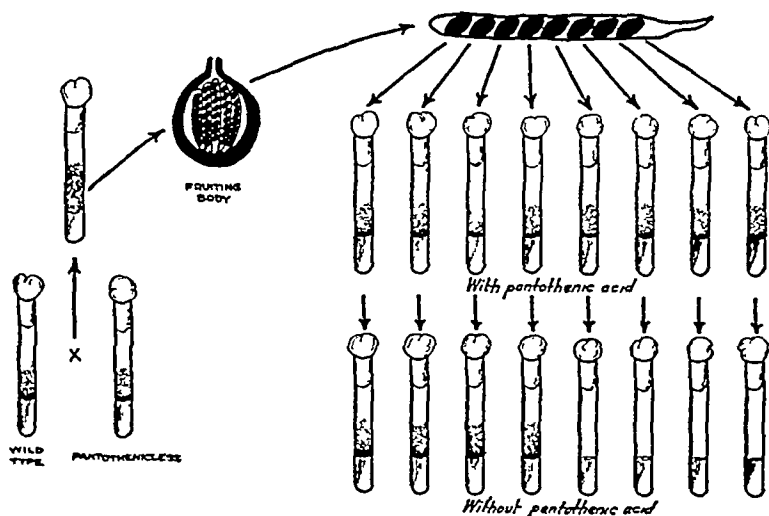


Fig 2 Procedure of following the inheritance of a mutant character in *Neurospora* Reproduced from the American Scientist by permission of the author and of Yale University Press

biotin (fig 1) Strains which are incapable of growing in this medium are tested systematically for their additional requirement

Over 90,000 cultures of *Neurospora* have been isolated from irradiated material and tested in this way (3) More than 500 of these cultures represent-

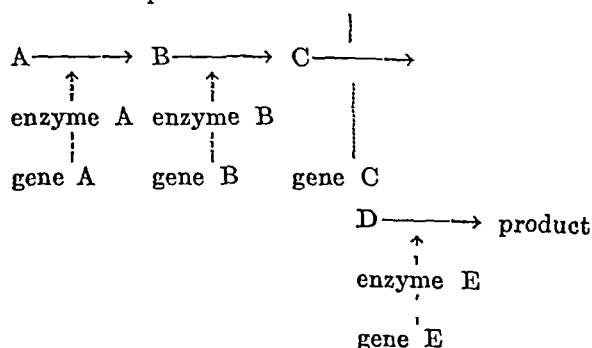
supply of a particular vitamin, amino acid or other growth factor Strains are now known with specific requirements for each of the accepted B-vitamins with the exception of folic acid, for most of the known amino acids, and for purines or pyrimidines (4, 5, 6) In certain of these mutant strains, the

synthesis of pyridoxin, riboflavin, adenine and uracil fail only under certain environmental conditions of pH or temperature, (4) The requirement of each strain is in practically every instance for a single specific substance. The fact that almost all the mutant strains so far obtained require known substances suggests that relatively few vitamins or amino acids essential for the growth of *Neurospora* remain to be discovered.

To complete the cycle, the genetic basis of each biochemical deficiency must be investigated. This is done by following the inheritance of the character in the progeny resulting from a cross of the deficient with a normal strain. If the strains grown from the 8 ascospores derived from such a cross show segregation into equal numbers resembling each parent (fig 2), the mutant strain differs from normal by a single gene. In the cases so far examined, each biochemical character has been so inherited. The results have therefore been in accord with the predicted 1 to 1 relation of gene and biochemical reaction. Each single gene mutation is associated with a single specific biochemical deficiency, and every biochemically different strain is also different genetically.

If the specific biochemical deficiencies of these mutant strains represent alterations or inactivations of specific enzymes concerned in synthetic reactions, the detailed study of their metabolism should permit the closer scrutiny of the predicted 1 to 1 relation of gene to enzyme. Of more immediate concern to the present discussion is the use of such mutant strains as biochemical tools in studying metabolism. Each mutant represents a strain in which a genetic monkey wrench has been thrown into the metabolic machinery of the cell—not thrown at random, but in such a way as to affect only single specific enzymatic reactions. The heritable alterations so produced then permit the biochemical analysis of the processes involved in a given biosynthesis, by means of a direct biochemical comparison of the mutant with the normal strain.

The biochemical potentialities of such analyses can perhaps best be pointed out from a consideration of the following hypothetical biosynthetic reaction sequence:



This is only one of the possible sequences, others might consist of converging or of diverging sequences. The example given illustrates a possible relation of gene to enzyme to reaction, and suggests some of the biochemical consequences of mutation of gene C to the inactive form c, resulting in the failure of the corresponding enzyme C, and in the consequent failure of the conversion of intermediate C to precursor D. Tests of these consequences can be used by the geneticist as criteria for the validity of the general concepts. If these concepts are correct the biochemist can use such mutant strains in the study of biosynthetic reactions.

The main assumptions are:

1 The series of biochemical reactions in a given biosynthesis involve the cooperation of a corresponding series of enzymes and genes.

TABLE I

Intermediates produced by mutant strains of Neurospora

STRAIN	REQUIREMENT	SUBSTANCE PRODUCED	BIBLIOGRAPHIC REFERENCE
9185	Thiamin	Pyrimidine + thiazole	12
14558	Thiazole	Pyrimidine	12
5531	Pantothenic acid	Lactone + β alanine	13
10575	Indole	Anthranilic acid*	7
47904	Dimethylamino ethanol	Monomethyl amino ethanol*	11
4540	Nicotinic acid	Unidentified precursor*	14

* Substance isolated in pure state

2 The production of each enzyme is controlled by a specific gene, with the converse proposition that each different gene controls a different enzyme, and consequently a different biochemical reaction.

The predicted biochemical consequences, susceptible to direct test are:

1 Any one overall sequence can be blocked at different biochemical steps as the result of the mutation of different genes.

2 An intermediate appearing in the sequence after a blocked reaction should approximate in activity that of the final product, and one occurring before the block should be completely inactive, although it would be active for a strain with a block earlier in the sequence.

3 The production and accumulation of an intermediate as the result of a genetically blocked reaction might be expected, with the consequent possibility of its isolation and identification.

These possibilities and predictions have been rather thoroughly investigated and tested by means of mutant strains of *Neurospora* deficient in the biosyntheses of arginine (7), tryptophane

(8, 9), and of choline (10, 11) The synthesis of arginine in *Neurospora* has been shown to occur by way of ornithine and citrulline, with the first demonstration of the operation of an ornithine cycle in plants The synthesis of tryptophane in *Neurospora* takes place via anthranilic acid and indole Anthranic acid has been isolated as an intermediate in this synthesis The final coupling of indole with serine to form tryptophane provides a clear example of the synthesis of an amino acid by a mechanism other than amination of the keto acid Choline is formed by way of monomethylaminoethanol in *Neurospora*, and this intermediate compound has been isolated as a product of the appropriate mutant strain Similarly, a precursor of nicotinic acid in *Neurospora* has been isolated but not as yet identified These and some of the other examples of the demonstrated accumulation of intermediate compounds in mutant strains of *Neurospora* as demonstrated either by isolation or by biological tests are given in table I

In summary, the experimental evidence so far obtained by the genetic and biochemical examination of mutant strains of *Neurospora* supports the proposed hypotheses as to the relation of gene to biochemical reaction and fulfils the expected consequences of these hypotheses The examples given amply illustrate the experimental use of *Neurospora* as a biochemical tool in the study of biosynthetic reactions

That there are many further potential contributions of *Neurospora* to biochemistry and genetics is apparent from the foregoing general discussion Since some of these applications and potentialities will be considered in detail in the following papers in this symposium, they need only be briefly men-

tioned here An important development is the use of mutant strains of *Neurospora* for bioassays of vitamins and amino acids The single specific requirement of each strain, the simplicity of the assay techniques, and the availability of strains for the determination of substances such as inositol, choline, *p*-aminobenzoic acid, proline and leucine are important advantages The possibilities of combination of desirable qualities in double mutants produced by genetic methods are also significant Recent developments in this field will be discussed by Doctor Ryan

Several different experimental approaches to the problem of the nature of the relation between gene and enzyme have been developed with *Neurospora* The question, fundamentally one of the basis of protein specificity—"How does gene mutation affect or modify an enzyme?" is raised by the existence of temperature sensitive biochemical mutants Doctors McElroy and Mitchell will discuss their investigations of purine synthesis in *Neurospora* from this aspect The reciprocal question,—“Can gene mutation be influenced by altering the enzymatic pattern of the cell?” has been investigated by Doctors Emerson and Cushing This approach will be discussed by Doctor Emerson

In conclusion it is worth reemphasizing the need for, and potentialities of, the joint attack on the fundamental problems of metabolism and enzyme action by the geneticist and biochemist using the techniques of both In this attack, mutant strains of organisms such as *Neurospora* add to the biochemical and biophysical armament of the biochemist their biological complements, genetically controlled biological tools

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THE APPLICATION OF NEUROSPORA TO BIOASSAY

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The extent to which a mutant of *Neurospora* will grow is usually a function of the single compound it has been induced to require. The greater the amount of this substance, the larger is the mycelium produced, the higher the concentration of the substance, the faster growth takes place. Because of this relationship, *Neurospora* has been used to determine both vitamins and amino acids for which mutants are available. As criteria of growth three different responses of the mold have been measured.

One response is the final mass of mycelium produced after growth has been completed on liquid medium. This response has been used for the determination of leucine (1). The procedure involves the inoculation of the leucineless mutant of *Neurospora* into liquid medium containing varying amounts of protein hydrolysate or of leucine. Growth is allowed to progress at 30°C. for about one week at which time it is complete. By the use of tared sintered-glass crucibles for harvesting mycelial weights are obtained on given leucine concentrations with a standard deviation of less than 2 per cent. Over a range from 0.2 to 1.0 mg. of leucine the standard curve is linear and can be described by an equation

$$\text{mg. leucine} = 0.02335 \times \text{mg. mycelium}$$

Identical standard curves are secured from day to day so that conditions need be checked only occasionally. This procedure meets all the criteria set up by Snell (2) for establishing the reliability of a microbiological assay. In addition, proof that it measures the leucine content of the medium comes from a correspondence of values obtained by the *Neurospora* method and reliable chemical methods (table 1). It should be emphasized that, wherever possible, new microbiological assays should be tested with proteins for which there exist reliable figures obtained by other procedures (3).

When the *Neurospora* leucine method was first developed it was complicated by the presence of adaptations. These were cultures whose weights did not show the characteristic relation to the leucine content of the medium but were higher. Complete adaptations resembled the wild-type mold in growth while partial adaptations weighed only slightly more than the average weight in a comparable series. Table 2 gives examples of both types of adaptations in a series of similar leucineless cultures grown at 30°C. in the presence of different amounts of leucine. In the assay procedure the weights of adapted cultures were eliminated from consideration by an arbitrary statistical procedure.

An investigation of adapted leucineless cultures has shown that they are the result of the back-mutation of leucineless nuclei to the wild-type condition (4). The weight of an adapted or back-mutated culture depends in part upon the time at which the back-mutation occurred during the

TABLE 1
Leucine values determined on identical preparations of proteins by the Neurospora method compared with values obtained by reliable chemical methods

PROTEIN	METHOD	PER CENT LEUCINE
Gelatin	<i>Neurospora</i> (1)	3.6
Gelatin	Solubility product (22)	3.5
Egg albumin	<i>Neurospora</i> (1)	9.6
Egg albumin	Solubility product (22)	9.1
Horse hemoglobin	<i>Neurospora</i> (1)	15.7
Horse hemoglobin	Isotope dilution (23)	15.1
β lactoglobulin	<i>Neurospora</i> (19)	15.4
β lactoglobulin	Isotope dilution (23)	15.6

TABLE 2
Complete and partial adaptations of leucineless Neurospora

FLASK NUMBER	MG. MYCELIUM ON DIFFERENT AMOUNTS OF LEUCINE		
	0.25 Mg.	0.50 Mg.	1.00 Mg.
1	9.8†	17.5	32.7
2	7.3	17.4	32.1
3	7.3	44.8*	32.9
4	7.3	19.0†	31.2
5	10.2†	17.8	33.2
6	20.8†	17.2	33.5
7	7.3	17.5	34.6
8	7.1	18.0	32.6
9	8.0	20.1†	35.4
10	50.3*	17.3	35.1
Average wt.	7.4	17.5	33.3

* Complete adaptation
† Partial adaptation

growth of the culture and, consequently, upon the length of the period during which it was growing like wild-type, independent of leucine. It also depends upon the chance that a back-mutated nucleus will be selected for and form a population of wild-type nuclei which overgrew the culture. This chance is a function of the competition which has been shown to occur in a mixture of leucineless

and back-mutated nuclei. Leucineless nuclei have a selective advantage over back-mutated nuclei in the presence of leucine. They can actually stop the growth of mycelium which has begun to grow independently of leucine because of the presence of some back-mutated nuclei. Large mycelial masses with many leucineless nuclei are more unfavorable for the escape of back-mutated nuclei than small mycelial masses. This explains the somewhat lower incidence of mutation on large amounts of leucine. These factors, then, determine the distribution of the weights of adapted cultures between the weight of the leucineless mold and that of wild-type and, hence, explain the occurrence of partial and complete adaptations.

Fortunately, the frequency of adaptation like the frequency of mutation is reduced by a decrease in temperature. By changing the assay conditions from 30°C to 25°C the percentage of cultures which adapt drops from 14 to 3 per cent. Since the final mycelial weights of the leucineless mold are the same at these temperatures, running the assay at 25° or 20° simply reduces the complication of adaptation.

Regnery (5) has presented some interesting data on the bioassay of intact protein molecules for leucine by allowing leucineless *Neurospora* to degrade the protein by its own digestive mechanism. His preliminary values indicate a complete recovery of leucine from casein. This direct procedure needs further investigation.

Another dry weight method which is precise and apparently reliable has been developed by Doermann (6). In many ways this is similar to the leucine method but since the lysineless mutant of *Neurospora* is specifically inhibited by arginine this amino acid must be removed by precipitation as the silver salt or by destruction with arginase. *Neurospora* dry weight methods are also available for the assay of pyridoxine (7, 8, 9, 10), p-aminobenzoic acid (10), inositol (10, 11, 12), choline (12, 13, 14, 15) and biotin (10, 14). These methods differ in many details from the *Neurospora* leucine method and also among themselves. For example, most investigators find it satisfactory to harvest the mold by fishing it from the liquid, pressing it between filter paper and drying it with heat. However, this method has not been found satisfactory for all purposes in all hands and the use of sintered glass crucibles dried in a vacuum over calcium chloride is sometimes preferred (16). Nevertheless, most of these methods have been used by at least two independent investigators and are claimed to be satisfactory. All of the dry weight methods theoretically depend upon the final mycelial weight being a function of the amount of required substance in the medium. The mold grows until the limiting substance is depleted. In the case of the leucineless mutant, when the final

weight of mycelium has been produced on a limiting amount of leucine, the sterile-filtered medium will not support the growth of a new inoculum of leucineless mold unless further leucine is added. The growth curve in liquid medium is such that a good approximation of final growth is made at 30°C on the higher leucine concentrations only after about 6 days. For the duration of incubation in the leucine assay 8½ days was chosen (1). Apparently because of the shape of the growth curve of the lysineless mutant, Doermann (6) found that a reduction in the variability of his assay could be achieved by increasing the period of incubation from 3 to 7 days. It is likely that the precision of other *Neurospora* assays, which range in accuracy from ± 2 to ± 20 per cent, could be similarly improved if speed can be sacrificed. The precision that can be obtained by the dry weight method is a definite advantage. The other major advantage is the simplicity of the procedure. The medium is simple and such factors as the inoculum age and size often need not be accurately controlled. Since the result is primarily a function of amount of limiting substance, and not concentration, many factors may vary within broad limits.

As the second criterion of growth the rate of progression of mutant *Neurospora* has been measured on an agar surface. This method has been used for the assay of p-aminobenzoic acid. The mold can either be grown in petri dishes, where the diameter of the colony is measured (17), or in special horizontal tubes half-filled with agar (18). The inoculum is introduced at one end of the tubes and the position of the growing frontier is marked on the tubes at various times. When distance covered is plotted against time a straight line is produced, the slope of which is the rate of growth. The rate of growth is indefinitely constant because the frontier is continually transplanting itself onto fresh medium. The rate of growth of mutant strains of *Neurospora* is a function of the concentration of required substance in the medium. When the rate of growth is rapid, and it may sometimes be as high as 5.2 mm/hr., the precision of duplicate runs is very high. But on very limiting concentrations of a required substance the variability may exceed ± 15 per cent (see also (6)). Further investigation may tell whether this variation is inherent in the method.

The newest method for using *Neurospora* to determine growth factors involves the germination of asexual spores or conidia. This work has been done in co-operation with Dr. Erwin Brand of the College of Physicians and Surgeons. Conidia from, for example, a prolineless mutant remain inactive for a matter of days unless some proline is provided in the solution. When proline is present the conidia germinate and extend finger-like hyphae which are easily discernible under the

water immersion lens of a microscope. The percentage germinated is a function of both time and proline concentration. When measured at a given time, such as 3 hours, the relationship shown in figure 1 is obtained. The per cent germination is a function of proline concentration. This response is very sensitive. In figure 1, 0.2 γ proline/cc is being measured but, since only enough fluid for examination under the microscope is required, 0.1 cc volumes are routinely used. Hence as little as 0.02 γ of proline is actually being measured. This is not necessarily the lower limit of the assay for speed and sensitivity are inversely related. The variability of these percentages is less than ± 5 per cent and is largely a function of errors in sampling conidia for examination. The age of the conidia and their concentration influence the rate

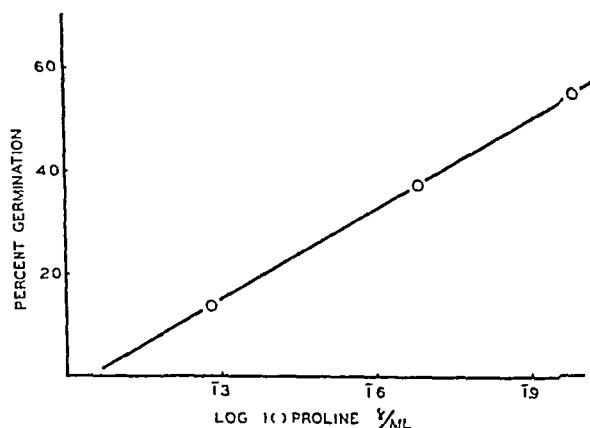


Fig 1 The relation of germination of conidia of the prolineless mutant of *Neurospora* to the concentration of proline in the medium. The measurements were made after 3 hours at 25°C

and amount of germination and must be carefully controlled. Thus far we have found it advisable to run a standard curve with each conidial assay. Results with conidia from the lysineless and the leucineless mutants of *Neurospora* are similar to those shown in fig 1 for the prolineless mutant—the rate of germination is a function of the concentration of the material these mutants have been induced to require.

The advantages of this method are its sensitivity, precision and speed. But there is a complication. Other amino acids exert a non-specific inhibition of germination not only of mutants but also of the wild type mold which requires no exogenous amino acids for growth. For example, fig 2 shows the inhibition of germination of the wild-type mold by various mixtures of amino acids. Thus it appears that equimolar amounts of glycine or mixed amino acids from β -lactoglobulin exert equal inhibitory effects. The same is true for amino acid mixtures containing only arginine and glutamic acid. Apparently the inhibition is a function

of the molar concentration of amino acids and not dependent upon any specific amino acid. Glycine itself is as inhibitory as a mixture of amino acids.

Consequently, in order to determine the leucine content of β -lactoglobulin, a molar concentration of glycine equal to the molar concentration of amino acids in the β -lactoglobulin hydrolysate being assayed, was introduced into the standard leucine solutions. The result was a leucine content of 15.3 per cent. When a β -lactoglobulin-like amino acid mixture was incorporated in the standard,

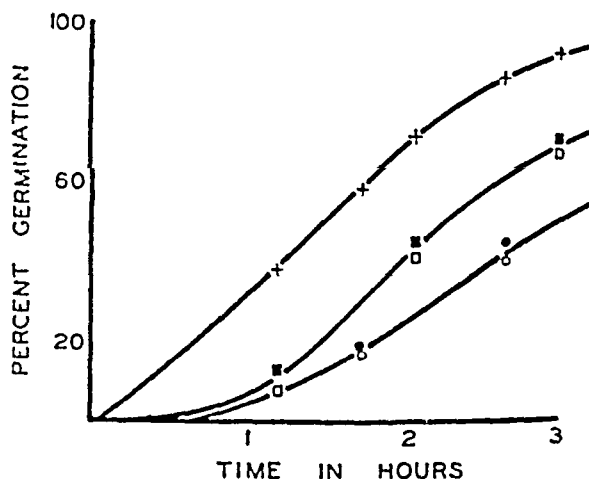


Fig 2 The per cent germination of wild type conidia in various mixtures of amino acids. Pluses represent germination in the absence of amino acids. Open squares represent germination of spores in the presence of 25.5 γ of hydrolyzed β -lactoglobulin per cc. Solid squares represent germination in a mixture of amino acids made up to duplicate 25.5 γ of hydrolysate per cc. (19). Open circles represent germination in 76.4 γ of hydrolyzed β -lactoglobulin per cc. Solid circles represent germination in the presence of 38.2 γ of hydrolyzed β -lactoglobulin per cc plus an amount of glycine (25.3) equal to the moles of amino acid in another 38.2 γ of β -lactoglobulin.

15.2 per cent leucine was obtained, when glutamic acid and arginine were incorporated in the proper molar concentration, 15.4 per cent was obtained. These values are similar to the 15.4 per cent leucine found in β -lactoglobulin by the *Neurospora* dry weight method (see table 1). Hence, it is established that the conidial assay procedure is reliable when amino acid inhibition is nullified by the incorporation of glycine in the standard solutions.

The solution of the problem of inhibition by other amino acids is obviously facilitated by our knowledge of the complete amino acid composition of β -lactoglobulin (19). The question arises whether it can be solved in the conidial assay of proteins whose composition is unknown. There are at least three ways of solving this problem. The

first is to incorporate in the basal medium a concentration of glycine so large that the addition of other inhibitory amino acids in the protein hydrolysate have no appreciable further effect upon germination. This, in principle, is what is done in amino acid assays by the use of the lactic acid bacteria. Figure 3 shows the inhibition of *Neurospora* germination by different amounts of glycine. The asymptote is not reached until germination is inhibited about 90 per cent. Therefore, incorpora-

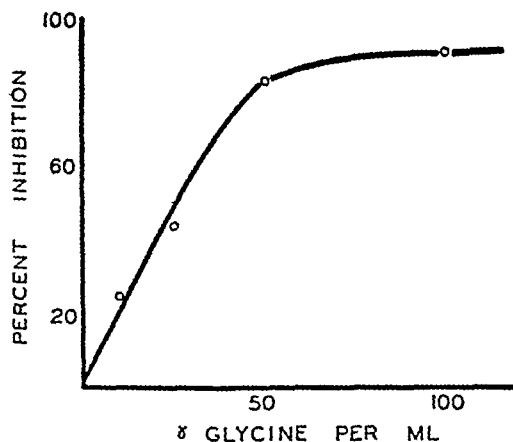


Fig 3 The per cent germination of conidia from the leucineless mutant of *Neurospora* after 5 hours at 25°C in the presence of 1 γ l(+) leucine and various concentrations of glycine

tion of about 75 γ of glycine per cc of basal medium would result in a per cent germination so small that the assay would not be feasible. A second solution would be the determination of, for example, the per cent proline at different levels of protein hydrolysate. The higher the concentration of protein hydrolysate the greater the inhibition and the smaller the per cent proline found. When such data are plotted as log per cent proline

against hydrolysate concentration it is possible to extrapolate the straight line obtained back to the zero protein hydrolysate level. Such an extrapolation should intercept the per cent proline axis at the true percentage of proline in the hydrolysate. We have attempted to use this method but find the precision of the conidial assay to be insufficient for an accurate determination of the leucine content of β-lactoglobulin. The third solution of the problem of amino acid inhibition is the same as was used for the determination by conidial assay of the leucine content of β-lactoglobulin, whose amino acid composition is known. The average residue weight of most proteins varies very little, about 2 per cent among fourteen proteins for which this value was obtained from the literature (20, 21). Therefore, the molar concentration of amino acids present in hydrolysates of the same amount of most proteins would be approximately equal. For the conidial assay of leucine in 11.8 γ of β-lactoglobulin per cc 7.9 γ of glycine per cc are incorporated in the standard solution. It should be possible to assay similar amounts of other proteins by introducing similar amounts of glycine into the standard solutions. From Fig 3 it can be seen that in the range of 8 γ of glycine per cc relatively large differences in glycine concentration will not result in significant differences in per cent germination. At the present time, in collaboration with Dr Brand the possibilities of this approach are being examined.

In summary, there are three general methods for using *Neurospora* to determine vitamins and amino acids. The dry weight method has, in the largest number of instances, been shown to be simple, precise and reliable. The rate of growth method is relatively unexplored. The new conidial assay method is the most sensitive and rapid. The entire assay can be completed in a day and it will determine as little as 0.01 γ of amino acid. Preliminary investigations indicate that it is precise and reliable.

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ADENINE-REQUIRING MUTANTS OF *NEUROSPORA CRASSA*¹

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Although adenine and some of its derivatives have been known as constituents of biological systems since 1850 (1), the biological mechanisms of fabrication of these compounds have remained obscure. Early work by Rose and Cook (2) indicated that the purines arise as metabolic products of histidine but more recent work by Burnes and Shoenheimer (3) has demonstrated that histidine is not used directly by rats for the biosynthesis of adenine. These investigators have also shown that ammonia nitrogen readily enters into tissue purines and that the purines exist in a dynamic equilibrium with a "labile nitrogen pool" in a manner analogous to certain amino acids (1).

The isolation, in this laboratory, of forty-five independently occurring mutants of *Neurospora crassa* that have growth requirements for adenine or related compounds, has presented an excellent opportunity for further studies on the mechanisms of biosynthesis of these purines. In addition, some of the strains are useful for bioassay purposes. The methods of production of these mutants, the techniques and value of genetic analysis, and the many biochemical applications of *Neurospora* mutants have been summarized in recent reviews by Beadle (5, 6) and in a paper by Beadle and Tatum (7). One of the adenine requiring mutants (number 3254) has been described by Pierce and Loring (8).

Experimental Basal medium. The composition of the basal medium used for *Neurospora* has been presented a number of times, but is reproduced in table 1 for convenience. The trace element solution is made up of the following compounds dissolved in one liter of distilled water: sodium tetraborate, 88 mgs; ammonium molybdate, 64 mgs; ferric chloride, 500 mgs; zinc sulfate $7H_2O$, 2 g; cupric chloride, 270 mgs; manganous chloride, 45 mgs.

Stock cultures may be maintained on this medium supplemented with adenine and solidified with 2 per cent agar. Better sporulation is obtained on a modified medium supplemented with yeast and malt extracts, vitamins, and hydrolyzed casein (7).

Qualitative growth.—All forty-five mutants have been tested qualitatively for growth on the basal medium supplemented with one of the compounds

adenine, hypoxanthine or guanine. All respond to adenine, all but two (11206 and 11115) to hypoxanthine and none to guanine. None of the mutants grow on a mixture of the known B vitamins or on hydrolyzed casein. Thirty-eight of the mutants were tested on a medium supplemented with urocanic acid (imidazole acrylic acid) and all failed to grow.

On the basis of growth characteristics and preliminary genetic analyses, eight of the mutants were selected for detailed investigations. The isolation numbers of this group are 3254, 27663, 28610, 35203, 11206, 11111, 70001, and 71101. All eight strains utilize adenine, adenosine, adenosine-

TABLE 1
Composition of Basal Medium

Ammonium tartrate	50 g
Ammonium nitrate	10 g
Potassium dihydrogen phosphate	10 g
Magnesium sulfate	0.5 g
Calcium chloride	0.1 g
Sodium chloride	0.1 g
Sucrose	15.0 g
Biotin	50 μ g
Trace elements solution	10 ml
Distilled water to	1.0 liter

3'-phosphate, adenosine-5' phosphate, adenosine 5' triphosphate, coenzyme I, coenzyme II, ribose nucleic acid, desoxyribose nucleic acid. In addition, all except 44206 utilize hypoxanthine, inosine, and inosine-3' phosphate. Compounds tested that did not promote growth of any of the eight mutants were histidine, urocanic acid, xanthine, guanine, guanosine, parabanic acid, uric acid, allantoin, alloxan, alloxantine, urocanic acid, uracil, cytosine, thymine, di-pyruvildureide, urea, pyruvic acid, oxalacetic acid, beta-alanine, oxalic acid, barbituric acid, oxyadenine,² oxyadenine-riboside and 2-oxy,6,8-diaminopurine. The last three compounds were obtained through the kindness of Dr. Joseph R. Spies (21).

Quantitative Growth.—Growth curves showing the response of the eight mutants listed above to adenine are presented in fig. 1. The curves are

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² Loring and Pierce (8) reported that adenine could be replaced by oxyadenine for promoting growth of mutant 3254. Doctor Loring generously furnished a sample of the active material, which he had obtained from Buell (22), and a determination of its absorption spectrum demonstrated that the substance was adenine rather than oxyadenine.

quite reproducible for each strain. Reisolations of 3254, 71104, and 44206 by outcrosses to wild type did not change the growth characteristics. All of

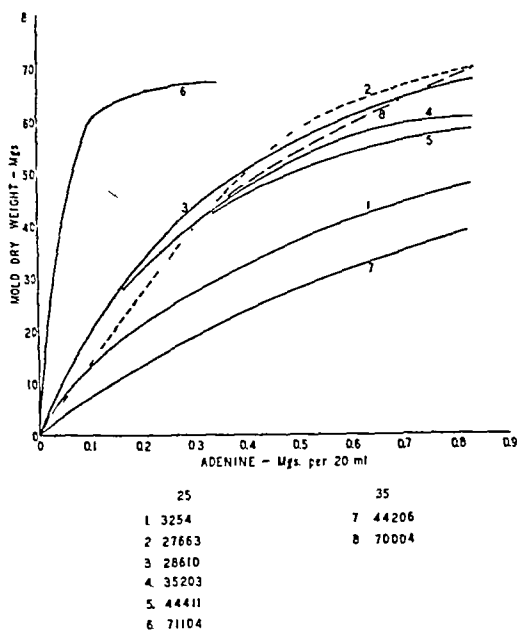


Fig 1 Growth curves of eight mutants of *Neurospora*. The curves were determined for an 84 hour growth period at the temperatures noted in the figure.

TABLE 2

Comparative activities of adenine, hypoxanthine and the corresponding nucleotides and nucleosides

STRAIN	TEMPERATURE °C	HOURS OF GROWTH	Compounds				
			MOLES EQUIVALENT TO 1 MOL OF ADENINE FOR GROWTH				
			Adeno- sine	Adeno- sine 3' Phos- phate	Hypo- xan- thine	Inosine	Inosine 3' Phos- phate
28610	25	84	1.07	1.60	0.98	1.10	1.30
28610	25	130	1.02	1.25	1.00	1.03	
28610	35	84	1.04	1.30	0.98	1.07	
44206	35	84	1.00	1.10	0.0	0.0	0.0
27663	25	84	1.10	1.33	1.00		1.25
35203	25	84	1.09	1.37	1.02		1.30
44411	25	84	1.08	1.08	0.98		1.25
70004	35	84	1.05	1.00	0.97		1.25
71104	25	84	5.00	5.50	1.80		4.60
3254	25	84	1.80	2.00	0.94		2.50

the mutants respond to adenine nucleotides and nucleosides, and seven respond to the corresponding derivatives of hypoxanthine. The comparative activities of these compounds are given in table 2. Activities are given in terms of moles of compound

required to give the same growth as one mole of adenine under conditions defined in the table.

Genetic Analysis—Two general methods are available for determining genetic differences in *Neurospora*. The first is dependent on heterocaryotic (9, 10) or symbiotic growth of two mutants placed together in a culture medium that will not support the growth of either mutant alone. Resulting growth under these conditions indicates that different biosynthetic reactions are blocked in the two strains. Growth results when sterile basal medium is inoculated with conidia from strains 28610 and 27663. The remaining 43 mutants were inoculated in combination with each of the above two in 20 ml of medium containing 0.03 mg. of adenine. This quantity of adenine is sufficient to allow germination of the spores but only a very small amount of mycelial growth, thus producing optimum conditions for initiating symbiotic or heterocaryotic growth. Of the total number of mutants, five grew in combination with both 28610 and 27663 and are thus different from both. Twenty-one strains grew in combination with one but not the other of the controls, indicating that each of these may be a genetic duplicate of 28610 or 27663. The remaining seventeen strains failed to grow in combination with either control. Since some genetically different strains do not grow symbiotically, these mutants cannot be classified by the experiments.

The eight mutants discussed in the section on quantitative growth, when crossed to the parent wild-type strain, yielded normal eight spored asci with four wild-type and four mutant spores in each. At least twenty asci were isolated from each cross. This is a sufficient number to demonstrate a high probability that each mutant differs from the parent strain by a single Medelian unit or gene.

Applying the second method of genotype determination (11, 12, 13, 14) the eight mutants selected were then crossed in all combinations among themselves and the results are presented in table 3. Asci with two or four wild-type spores demonstrate mutation of different genes in the two strains crossed. A high ratio of asci containing eight mutant spores to asci containing wild-type spores indicates that the mutated genes of the two strains have nearly the same locus on corresponding chromosomes. If no wild type spores are obtained from a large number of asci it is necessary to conclude that the mutants crossed represent the same genotype so far as can be determined by the genetic method. As an added check on the validity of the results tabulated, a double mutant was taken from an ascus from each cross and in turn crossed to the wild-type parent. The two original mutants were then reisolated. The data obtained by the above means were insufficient for genetic analysis in the crosses 27663a × 44206A, 44206A

× 44411a, 35203A × 71101a, and 27663a × 70001A. Spores were therefore isolated at random from these crosses. The first case gave five wild-type spores from 633 spores, the second gave 83 wild-type spores from 212 spores, and the third gave 7 wild types from 137 spores. Genetic differences are indicated in all three cases. A double mutant was isolated in the first two cases. Seven hundred and fifteen spores were taken at random from the

TABLE 3

Summary of crosses of eight adenine mutants among themselves

STRAINS CROSSED	NUMBR OF ASCI OR SERVED	ASCI WITH 2 WILD TYPE SPORES	ASCI WITH 4 WILD TYPE SPORES	ASCI WITH 5 MUTANT SPORES
3254a × 27663A	17	4	8	5
3254a × 28610A	15	8	5	1
3254a × 38701A*	7	1	6	0
3254a × 44206A	20	4	12	4
3254a × 44411A	19	14	1	4
3254a × 70004A	17	8	6	3
3254a × 71101A	20	1	8	11
27663A × 28610a	11	3	6	2
27663A × 38709a*	10	3	3	4
27663A × 44206a	9	0	0	0
27663a × 44206A	40	0	0	40
27663A × 44411a	13	7	2	4
27663a × 70004A	25	0	0	25
27663A × 71101a	13	5	6	2
28610A × 35203a*	4	2	2	0
28610A × 44206a	14	7	1	5
28610A × 44411a	14	8	2	4
28610a × 70004A	3	2	1	0
28610A × 71101a	12	1	7	4
35203*a × 44206A	4	1	1	2
35203*a × 44411A	10	6	4	0
35203*a × 70004A	6	2	0	4
35203* × 71101	0			
44206A × 44411a	0			
44206A × 70004a	15	1	0	14
44206A × 71101a	10	1	5	4
44411A × 70004a	14	8	2	4
44411A × 71104a	18	10	4	4
70004A × 71101a	9	4	2	3

* Purple mutants of the same genotype

fourth cross (27663a × 70004A) without obtaining a wild-type strain. Although these two mutants differ physiologically (temperature sensitivity) as will be shown later, they appear to carry allelic genes.

The data from these genetic experiments demonstrate that seven genotypes are represented among the eight mutants that were subjected to a thorough analysis. By analogy with previous work on *Neurospora* these seven genotypes correspond to seven different biosynthetic reactions that

lead to the formation of adenine or its biological equivalent.

Distinctive Characteristics of Mutants—The growth of three of the mutants is markedly dependent on temperature. Mutants 11206 and 70001 grow in the absence of adenine, between the temperatures of 10° and 26°C nearly as well as does a wild-type strain. Adenine is synthesized by the strains during growth in this temperature range, a fact demonstrated by isolation of adenine as a pure compound and by bioassay using one of the adenine requiring mutants. In the temperature range of 33°C to 40°C these two mutants are not able to carry on biosynthesis of adenine and growth becomes a function of the quantity of the purine supplied, as shown in the curves of fig. 1. Limited ability for synthesizing adenine can be demonstrated in the intermediate temperature range of 26° to 33°C. Mutant 3251 is also temperature sensitive, but only in that it grows very poorly at 35°C even on an excess of adenine.

Strain 71101 possesses the ability to synthesize part of its adenine requirement at both 25° and 35°C. The curve given in fig. 1 represents a growth period of four days at 35°C. This curve shifts a great deal with time, with an increased sensitivity to adenine in a longer growth period. That this is due to a synthesis of adenine, is demonstrated by the following experiment. Strain 71101 was grown for 7 days on 500 ml of basal medium supplemented with 2.0 mg of adenine. The resulting mycelium weighed 2.3 gm (dry) and contained 9.5 mgs of adenine by bioassay with mutants 44206 and 28610.

Mutant 35203 and its genetic replicates (four in number) produce, during growth, a brilliant red-purple pigment. The color-producing character segregates in crosses involving these mutants along with the single gene, adenine requiring character. The purple mutants give all purple progeny when crossed among themselves. A maximum quantity of pigment is produced by the strains when sufficient adenine is supplied to give about half maximum growth. With excess adenine, only a small amount of pigment is formed. The colored material appears first as a highly soluble pigment, but in older cultures it appears largely as red-brown or black granules in the mycelium. Granules may be observed undergoing brownian movement in the mycelial vacuoles. In this water-insoluble form quantities may be obtained as high as 15% of the dry weight of the mold. These experiments and others to be described indicate that the pigment arises as an abnormal metabolic product from a labile adenine precursor that accumulates as a result of the genetic block in adenine synthesis. The chemical nature of this compound will be considered in a subsequent publication. It is of special importance to note that mutant 44206 can

also produce the purple substance under appropriate conditions even though it does not normally do so. The pigment is formed in this mutant when it is grown at 37°C in the presence of yeast extract that contains a suboptimal amount of adenine. The yield of colored material is far less than in the mutants represented by the genotype of 35203.

Biosynthesis of adenine—The biosynthesis of adenine cannot be discussed without a consideration of the corresponding nucleoside and nucleotides. Indeed, as has been indicated by recent investigations,³ at least the last synthetic step takes place with the ribosides rather than with the purines themselves. In the absence of more extensive information biosynthesis will be dealt with in terms of formation of adenosine.

It has been mentioned above that mutant 44206 and its genetic duplicate 44115 utilizes adenosine and not inosine, while the other mutants of the group can use either with equal facility. It is therefore evident that strain 44206 is deficient in an ability to aminate inosine to give adenosine and this mutation must therefore represent the last stage in adenosine synthesis. However, such a reaction requires a considerable amount of energy, and it cannot be determined at present whether the mutation is concerned directly with amination or with a coupled system supplying the necessary energy for amination.

As has been shown in an earlier section, the compounds tested that do not contain adenine or hypoxanthine do not promote the growth of any of the seven mutants of different genotypes. These compounds include guanine, guanosine, xanthine, histidine, and urocanic acid. Numerous attempts have been made in an effort to detect the accumulation of adenosine precursors that might result from the genetic blocks of the seven different reactions indicated by the genetic analyses. Since such accumulation has not been observed it is concluded that the intermediate compounds are biologically labile or are not formed in detectable quantities.

Genetic evidence has indicated the existence of seven reactions leading to the biosynthesis of adenosine. Such reactions may fall in a consecutive order or in converging series. Some evidence on this point has been obtained by utilization of the pigment producing properties of double mutants of the purple strain (35203) and a non purple strain. Results are given in table 4.

The existence of non purple double mutants suggests that the two reactions concerned fall in a series with the reaction leading to pigment formation coming second. The fact that the pigment is

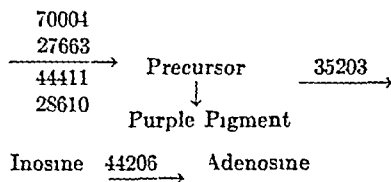
produced by the double mutant 35203-44206 can be explained either on the basis of reactions in series, with the reaction blocked in the purple strain coming first, or on the basis of reactions of converging series. Since the single mutant 44206 can produce the pigment under appropriate conditions and since this strain does not utilize hypoxanthine, the first suggestion appears to be the correct one.

TABLE 4
Pigment production by double mutants

DOUBLE MUTANT	25 C	35 C
26610 and 35203	non purple	
27663 and 35203	non purple	
4411 and 35203	non purple	
70004* and 35203	purple	non purple
44206* and 35203	purple	purple

* Temperature sensitive mutants

The known facts concerning the mechanism of adenosine biosynthesis in *Neurospora* may be summarized as follows:



Strains 3254 and 71104 cannot be definitely placed in the series. The chart indicates only the arrangement of the mutants in a series of biosynthetic reactions and does not refer to the number of steps in each conversion. In addition the mutants 27663, 28610 and 4411 presumably represent different biochemical reactions but no data are yet available to indicate the order for the reactions controlled by these strains.

Bioassay for Adenine—Mutants 28610 and 44206 are suitable for bioassay purposes. By utilizing both of these mutants it is possible to determine adenine (44206) and adenine plus hypoxanthine (28610). Such an application is presented in table 5, for the determinations of these two purines in samples of nucleic acids. The ribonucleic acid was obtained from Eastman Kodak, Rochester, New York and the deoxyribonucleic acid (fish sperm) was obtained through the generosity of Dr. Hubert S. Loring, Stanford University, California. The assays were carried out on both hydrolyzed and intact nucleic acid. Hydrolyzed samples were prepared by heating the nucleic acid sample at 100°C for one hour with 50 parts of a solution 1 N in HCl and 10 N in formic acid, according to the procedure of Graff and Maculla (15). These assays are conveniently carried out by addition of sam-

³ Unpublished work in this laboratory has shown that *Neurospora* contains adenosine deaminase but not adenine deaminase.

ples, in 1 ml or less of water, to 20 ml of basal medium contained in 125 ml erlenmeyer flasks. The medium is inoculated with one drop of a dilute conidial suspension from the appropriate mutant strain. A control series containing from 0.1 to 0.8 mg of adenine is prepared for each assay. Examples of these growth curves are given in fig. 1. After the appropriate period of time at 25° (28610) and 35° (44206) the mycelial pads are removed with forceps, squeezed out on filter paper, dried on cardboard trays at 80°C, and weighed. The adenine or adenine plus hypoxanthine content of

Several tissues have been assayed for adenine plus hypoxanthine using mutant 28610. The hydrolysis procedure of Graff and Maculla (15) was utilized for preparation of samples. The tissues were hydrolyzed at 100°C for one hour with fifty parts of 10 *M* hydrochloric acid. After evaporation to dryness the residue was redissolved in water, neutralized with potassium hydroxide and diluted for assay. These results are given in table 6.

Discussion. Barnes and Schoenheimer (1) have demonstrated that urea and histidine do not take a direct part in the biosynthesis of adenine in rats

TABLE 5
*Adenine and hypoxanthine in nucleic acids**

MATERIAL	GROWTH PERIOD DAYS	MCS PER C OF ADF I F PLUS HXFO XANTHINE 28610	RECOVERY PER CENT 28610	MCS PER C OF ADENINE 44206	RECOVERY PER CENT 44206
1 Ribonucleic acid	3	51		20	
2 Ribonucleic acid	5	132		64	
3 Ribonucleic acid	7	150		83	
4 Ribonucleic acid-H ₂ Olyzed	3	100		90	
5 Ribonucleic acid H ₂ Olyzed plus 300 mgs /g adenine	3	454	95	336	80
6 Ribonucleic acid-H ₂ Olyzed plus 300 mgs /g hypoxanthine	3	498	104		
7 Sodium desoxyribonucleate	3	35		35	
8 Sodium desoxyribonucleate	5	66		68	
9 Sodium desoxyribonucleate	7	80		81	
10 Sodium desoxyribonucleate H ₂ Olyzed	3	125		88	
11 Sodium desoxyribonucleate-H ₂ Olyzed plus 300 mgs /g adenine	3	407	94	316	76
12 Sodium desoxyribonucleate H ₂ Olyzed plus 300 mgs /g hypoxanthine	3	419	95		

* Assuming a tetranucleotide structure for the nucleic acids the ribonucleic acid should contain 105 mgs of adenine per g and the sodium desoxyribonucleate 102 mgs of adenine per g.

TABLE 6
Adenine plus hypoxanthine in tissue extracts

MATERIAL ASSAYED	MG ADENINE PLUS HYPOXANTHINE PER GM (DRY WEIGHT)
Rabbit liver	5.2
Rabbit leg muscle	6.5
Rabbit kidney	8.0
Rabbit brain	1.5
Swiss chard	2.8
Neurospora (wild type)	5.2
Yeast extract	11.0

each sample is determined directly from the control curve. It is advisable to use several different dilutions of the same sample to give mold growth corresponding to different points on the control curve.

Mutant 28610 is satisfactory for the determination of adenine plus hypoxanthine in tissues and raw materials. Strain 44206, however, is inhibited by materials produced during the hydrolysis of many tissues. No satisfactory method has yet been devised for removal of these inhibitory substances.

and pigeons, and the experiments on *Neurospora* mutants are in agreement with these findings. In addition, guanine, uracil, thymine, cytosine and xanthine do not play an obvious role in the scheme of adenine synthesis in the mold. It appears probable that *Neurospora* does not contain an enzyme capable of catalyzing the dismutation of xanthine to uric acid and hypoxanthine though it has not been demonstrated that xanthine penetrates the cell membrane of the mold. In any case, there is no evidence for the existence in *Neurospora* of a purine metabolic system involving histidine, xanthine and uric acid such as is found in higher animals and it would appear that the two essential purines, adenine and guanine, arise from different and not closely related systems.

That the purple pigment is a reaction product of an intermediate in adenosine biosynthesis rather than the intermediate itself is shown by the fact that the substance does not support the growth of any of the mutants that have been genetically distinguished. However it is evident that the colored material is intimately related to adenosine synthesis since the ability to produce

color segregates in crosses with the adenine growth requirement. In addition, it is significant that several double mutants each involving the purple strain are incapable of producing the pigment. This finding can be reasonably interpreted by assuming that the mutations of the non-purple strains cut off the supply of material necessary for the synthesis of the pigment. Synthesis of relatively small quantities of pigment by mutant 44206 may be interpreted as a backing up of precursors down the synthetic chain to the extent that the equilibria are in favor of formation of some of the colored compound. Evidence based on the growth requirement (adenine but not hypoxanthine) places the 44206 mutation following the reaction blocked by the purple mutant (35203) and is thus in accord with the above interpretation.

A discussion of the temperature sensitivity as well as partial blocks in synthetic ability (mutants 44206, 70004 and 71104) must await further investigations. Several apparent manifestations of these two phenomena in *Neurospora* mutants have been described: *choliness* (16), *riboflavinless* (19), *pyridoxinless* (18), and *argininless* (19).

Investigations on the use of the *Neurospora* mutants for bioassays for adenine and hypoxanthine are not complete but preliminary data are presented. It appears that strain 28610 is satisfactory for use in assays for adenine plus hypoxanthine but the inhibitors encountered in using strain 44206 necessitate further investigations before this mutant will be satisfactory for adenine assays. However, both of these strains are available for application to assay problems.

The unexpectedly high values found for the hypoxanthine and adenine content of nucleic acids cannot be adequately interpreted since the preparations cannot be considered as pure chemical entities. Although mutant 44206 gives adenine values approaching the calculated adenine content of the nucleic acids recoveries of added adenine

are poor and assay data obtained with this mutant can not be considered significant. The high values found using mutant 28610 (adenine plus hypoxanthine) can be due to impure nucleic acid preparations or possibly they are correct, and knowledge of nucleic acid structure is insufficient. Evidence is against the suggestion that mutant 28610 responds to components of nucleic acids other than adenine or hypoxanthine since the other known aglycones have been shown to be without effect. Greenstein and Chalkley (20) have shown that tissues contain enzymes capable of deaminating the purines of intact nucleic acids, thus indicating that hypoxanthine may be a natural component of the nucleic acids.

SUMMARY

1 Forty-five independently occurring mutants of *Neurospora* have been shown to require adenine. Forty-three of these mutants also utilize hypoxanthine but none utilize guanine. Eight of the mutants were investigated more thoroughly and all failed to use on guanosine, uric acid, xanthine, histidine, urocanic acid and fifteen other compounds that might be considered to be related to the purines.

2 The nucleosides and nucleotides of the active purines as well as some more complex derivatives are utilized by the mutants.

3 Genetic analysis of eight of the mutants has demonstrated seven genotypes and further genetic and biochemical experiments have shown that at least three of the genotypes represent different reactions in a consecutive series leading to the formation of adenosine. Inosine has been shown to be a precursor of adenosine.

4 Mutant 28610 has been satisfactorily utilized for bioassays for adenine plus hypoxanthine. The use of strain 44206 for adenine bioassay necessitates the development of methods for removing inhibitors that are found in extracts and hydrolysates.

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ENZYME STUDIES ON A TEMPERATURE SENSITIVE MUTANT OF NEUROSPORA¹

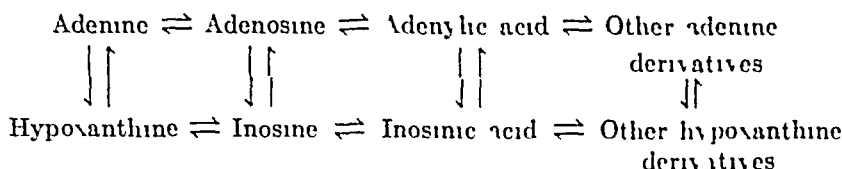
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Recent reviews by Beadle (1) (2) have summarized accumulated evidence which has led to the conclusion that most chemical reactions in living organisms are controlled by specific genes. It is presumed that a given gene serves as a model in determining the configuration of one enzyme and that this enzyme in turn acts as a catalyst for one reaction or type reaction. Although it has been assumed that the artificially induced mutants of *Neurospora* (3) (4) are unable to synthesize specific growth substances because of a gene inactivation and a corresponding enzyme deficiency, the problem has not been approached from the standpoint of investigations on the specific enzymes involved.

Since the demonstration of the absence of an enzyme in a mutant would constitute only negative evidence of the gene-enzyme relation, certain

The mutant selected for these investigations has been mentioned briefly in a previous report (6). This strain (44206) is unable to convert the purine hypoxanthine to adenine. This seemingly simple reaction involves the substitution of an amino group for an oxygen atom in the six position of purine. However, as implied by the work of Schmidt (7), the reaction is one requiring considerable energy, and it is therefore not unreasonable to postulate the existence of an unstable intermediate, in which case more than one enzyme would be involved. The problem is further complicated by the fact that adenine exists in living organisms in many chemical combinations. Some of the possible interrelationships of these substances to hypoxanthine derivatives are indicated as follows:



temperature sensitive *Neurospora* strains (5) (6) appeared to present the most suitable material for study. In one temperature range these mutants have nearly the same capacity for biosynthesis as the parent wild type strain, but they are unable to carry out one specific reaction in another temperature range. In terms of production of enzymes, several explanations of this phenomenon are possible.

1. A gene is altered by mutation in a manner such that an enzyme with an abnormal temperature sensitivity is produced.

2. A gene is altered in such a way that it no longer functions over the entire temperature range of growth of the wild type mold.

3. The organism has alternate pathways for synthesis of the required growth substance, and these systems operate in different temperature ranges. In this case one system is completely inactivated.

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At 35°C strain 44206 utilizes only the adenine derivatives, and it therefore appears probable that the reaction in question takes place with only one of the derivatives, i.e., the uncombined purine, the nucleoside, or a nucleotide.

Experimental Growth characteristics of strain 44206. The growth requirements and methods of culture for mutant 44206 have been described (6). The specific effects of temperature on the growth of this strain are indicated in figure 1. During growth at 25°C, adenine synthesis by the mutant has been demonstrated, but above 35°C the ability to make this compound is completely lacking. Growth of the mutant at 35°C in the presence of different quantities of adenine is shown in figure 2 (curve A). At this temperature the adenine supplied is used up in about three days, but, as shown in figure 1, even an excess of adenine fails to stimulate the mutant to grow as much as the parent wild type mold. New strains obtained through outcrossing the mutant to wild type had the same growth characteristics, indicating that the poor growth is specific to this particular strain. However, it has been shown that addition of the amino acid (1) histidine to the basal medium results in a sparing action with respect to the utilization of adenine or adenosine. Histidine is ineffective for growth promotion in the absence of ade-

nine This effect is indicated in figure 2 (curve H) Twenty other amino acids were tested separately and none of these produced a like result, though methionine and homocystine produced a small inconsistent effect Urocanic acid (imidazole

H M) Cystine had a slight effect, but other amino acids were inactive These included isoleucine, leucine, valine, tryptophane, arginine, threonine, lysine, phenylalanine, alanine, asparagine, glutamic acid, aspartic acid, glycine, proline, hydroxyproline, serine, tyrosine, norleucine, and norvaline

The combination of histidine and methionine produced no stimulating effect on the utilization of adenine by adenineless mutants that have the capacity for converting hypoxanthine to adenine, i e., strains 28610, 70004, and 35203 (6)

Adenine deaminases of *Neurospora* It has been indicated that the blocked reaction in mutant 44206 is concerned with the amination of hypoxanthine or a derivative thereof to give adenine or one of its derivatives Since considerable work has been done on enzymes catalyzing the reverse reaction (purine deaminases), investigations of enzymes of this type were undertaken as a primary step in studies of the gene enzyme relation in the temperature sensitive mutant 44206 Enzyme preparations were made as follows Mold was grown for enzyme extractions in five liters of basal medium (4) (6) containing 0.15% calcium carbonate After inoculation with conidia from the appropriate strain the mold was allowed to grow under forced aeration for 5 to 6 days at 25°C At the end of this time the medium had evaporated to approximately one liter The mold was removed by filtration through cheesecloth and the medium was discarded Following maceration in a Waring blender the mycelial mass was diluted with two volumes of 1/15 M disodium phosphate and allowed to autolyze for 16 hours at 25°C The pulp was then filtered off and discarded The filtrate was adjusted to a pH of 7.4, and the resulting flocculent precipitate was removed by centrifugation The resulting clear supernatant liquid was utilized as a source of deaminating enzymes Various other procedures were less satisfactory (7) (8)

One ml of this crude enzyme preparation will deaminate approximately 1 mg of adenosine in 1 hour Purification of the enzyme can be effected by adsorption of impurities on charcoal (norite) or permittit while the enzyme remains in solution Lead or alcohol can be utilized for precipitation of the adenosine deaminase, but the crude preparations were considered more suitable for preliminary investigations

Deamination was determined by bioassay using mutant 44206 to measure unreacted adenine and by the spectrophotometric method of Kalckar (9) A modification of the latter method for application to pH and temperature studies of adenosine deaminase from *Aspergillus oryzae* has recently been described (10)

Adenosine is rapidly deaminated by the enzyme preparations from mutant 44206 and from the wild

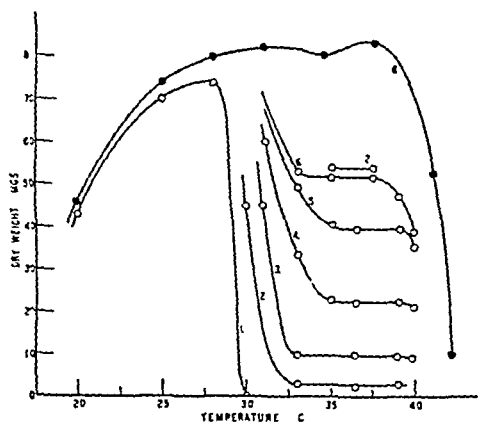


Fig 1 Temperature sensitivity of mutant 44206 The data are taken from five experiments using an 84 hour growth period in 20 ml of medium Curve 8 represents wild type *Neurospora* Curves 1-7 represent the following concentrations of adenine in mgs per 20 ml of medium 1-0.0, 2-0.05, 3-0.2, 4-0.6, 5-1.0, 6-2.0, 7-3.0

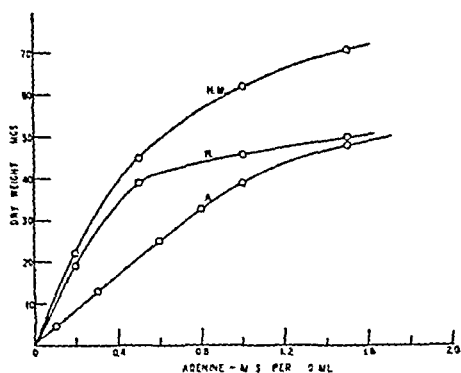


Fig 2 Growth curves of mutant 44206 Curve A—Adenine Curve H—Adenine plus 4 mgs of (l) histidine per culture Curve H M—Adenine plus 4 mgs of (l) histidine and 4 mgs of (l) methionine per culture Temperature 35°C

acrylic acid) was without activity In spite of the marked action of histidine the total maximum growth of the mutant remained abnormally low Since adenine plus hydrolyzed casein promoted growth comparable to that of the wild type strain, other amino acids were tested in combination with histidine and adenine Methionine and homocystine produced a marked stimulation (fig 2, curve

type *Neurospora* (Abbot 4A) Adenosine 3' and 5' phosphates are also deaminated but at a much slower rate, while adenine remains unchanged by the enzyme preparations. The rate of deamination of adenosine at various hydrogen ion concentrations is recorded in figure 3. These experiments were carried out at 35°C in 1/15 M phosphate buffer using a concentration of adenosine equivalent to 0.5 mg of adenine per ml of enzyme preparation (0.99 mg adenosine per ml). The rates were determined from a plot of the percent deamination against time. During the early phase of the reaction (20–30%) the plot gives a fairly good estimate of the rate, since this part

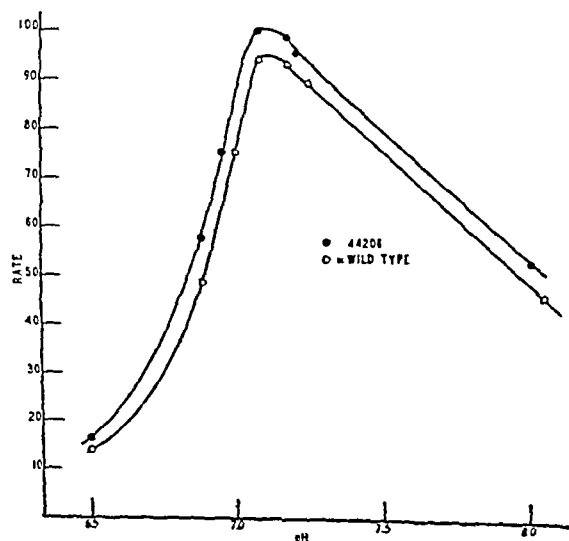


Fig 3 pH optimum of adenosine deaminase from *Neurospora*. Rate is given in terms of μg of adenosine deaminated in 10 minutes by 1 ml of enzyme preparation. The reactions were carried out at 35°C.

of the curve is essentially linear. The percent reaction at various times was determined spectrophotometrically.

The optimum pH for adenosine deaminase activity was found to be approximately 7.2. This optimum has been found the same for various enzyme preparations of different degrees of purity and agrees with the optimum of blood adenosine deaminase described by Conway and Cook (11). No difference was found between the pH optimum of the enzyme isolated from the wild type organism and the temperature mutant.

The activity of adenosine deaminase at different temperatures has been determined using the procedure described above. Phosphate buffer (pH 7.2) was employed. Figure 4 records the results for both the wild type and the mutant deaminases. The figure represents an average of three experiments for each of the deaminases. The slope of

the straight line obtained by a log plot of the deamination rates against the reciprocal of the absolute temperature gives a value for the activation energy of approximately 12,000 calories per mole for both, while the value of the energy of inactivation is around 60,000 calories. No difference was noted between the enzymes from the mutant and those from the wild type organism. The optimum temperature for the deaminase is approximately 39°C. Temperature curves at higher and lower hydrogen ion concentrations revealed a slight shift in the optimum, but again no noticeable difference could be demonstrated between the mutant and the wild type organism.

Temperature and pH characteristics for a deaminase of *Neurospora* acting on adenosine 3'-

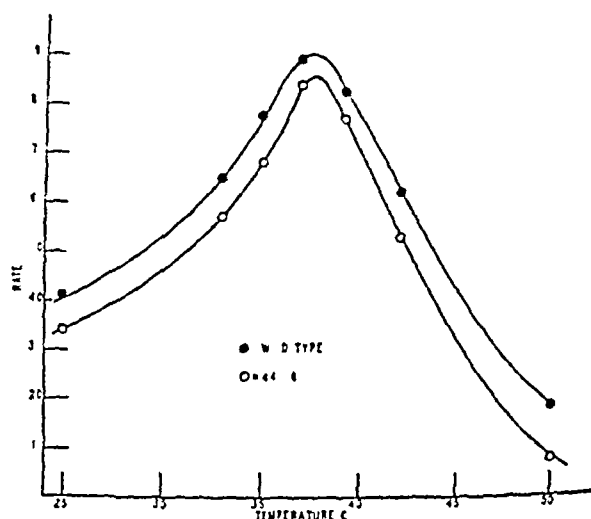


Fig 4 Temperature optimum of adenosine deaminase from *Neurospora*. Rate is given in terms of μg of adenosine deaminated in 10 minutes by 1 ml of enzyme preparation. The reactions were carried out at pH 7.2.

phosphate are identical with those of the adenosine deaminase, and it appears likely that the nucleotide is rapidly dephosphorylated and then deaminated as adenosine. No differences, in this respect, were found between the enzyme preparations from wild type and mutant 44206.

In order to test the hypothesis of presence of a heat labile gene in strain 44206, the mold was grown at 37°C on basal medium containing 50 mg of adenine per liter. This temperature was maintained throughout the process of enzyme preparation. Deaminase activity was found to be the same as that of preparations from the mold grown at 25°C.

Adenineless strain 28610 (requiring adenine or hypoxanthine) yielded enzyme preparations with deaminase activity identical with that from wild type and 44206.

Discussion From the data presented it is evi-

dent that the adenosine deaminase extracted from mutant 44206 and from wild type *Neurospora* are not significantly different. This enzyme is produced by the mutant when growth takes place either at 25°C or at 37°C. Furthermore, *Neurospora* does not contain adenine deaminase and probably does not contain adenylic acid deaminase. Thus, it appears that the deamination, and presumably the amination, takes place at the riboside level. It has not been possible to carry out the amination process *in vitro* and, since the kinetics of deamination are such that a considerable amount of energy must be supplied for the reverse reaction, it appears probable that the mutation has affected a coupled system or a completely different system rather than the one studied. The growth-stimulating effects of histidine and methionine are of special interest in this regard. These amino acids do not affect the utilization of adenine by other *Neurospora* mutants that require this purine, but do have the capacity to carry out the conversion of inosine to adenosine. It appears possible, therefore, that the system responsible for inosine amination also has some function in the metabolism of histidine and methionine. It is to be noted that adenine corresponds to an imino acid rather than an amino acid and no oxidation or

reduction need be involved in the conversion of hypoxanthine to adenine.

It was demonstrated by Rose and Cook (12) that the feeding of histidine to rats increased the excretion of purines, though the more recent work of Barnes and Schoenheimer (13) casts considerable doubt on any direct relationship of histidine metabolism to adenine formation. It is possible that a sparing action by histidine on adenine utilization, such as is found in the *Neurospora* mutant, is significant in this regard.

SUMMARY

1 *Neurospora* contains adenosine deaminase but no adenine deaminase. Adenylic acid is probably deaminated through dephosphorylation and action of the adenosine deaminase system.

2 Although strain 44206 is unable to aminate inosine to give adenosine, the adenosine deaminating enzyme is produced in a normal quantity by the mutant. This is evidently not the enzyme affected by the gene mutation in strain 44206.

3 Histidine and methionine have a marked stimulating action on adenine utilization by mutant 44206. It is suggested that the mutation of this strain affects a nitrogen transfer system that has a common function in the metabolism of adenine, histidine, and methionine.

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ALTERED SULFONAMIDE ANTAGONISM IN *NEUROSPORA*¹

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When microorganisms are cultured on a substrate which barely supports growth, it frequently happens that the organisms become adjusted in a way which permits enhanced growth. The original retarded growth may result from the inability of

the organism to utilize the substrate in its nutrition, in which case the appearance of more rapid growth frequently indicates that the organism has developed the capacity to utilize the substrate. In other instances the original poor growth may be the result of the toxicity of the substrate, in which case the adjustment permitting increased growth usually involves some change in the physiology of the organism which overcomes the toxicity of the substrate. In this paper we shall use

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the term "adaptation" to indicate all such changes in response of organisms to environmental conditions, regardless of the mechanisms that may be involved in the different examples

To understand the nature of any one adaptive change it is necessary to know just how the physiological set-up in the organism has changed. We should like to know if a new mechanism, presumably enzymatic, has developed, if an existing mechanism has been stepped up to a more efficient level of activity, or if an existing mechanism has been altered in its specificity, (e.g. a change in the substrate specificity of an enzyme). Further we should like to know which, if any, of such changes can occur without any change in the genetic background of the cell, which can occur only with an accompanying genetic change, and, if both alternatives exist, whether or not the two are in any way related. And finally we should like to know whether any of these changes result directly from the presence of the substrate, or are the result of accidental changes, genetic or otherwise, which are observable only in the presence of the substrate.

The studies to be reported represent a part of a program aimed at an understanding of the adaptive changes to sulfonamides occurring in the ascomycetous fungus *Neurospora*. Because of the numerous analogs, differing in chemical configurations, the sulfonamides offer an opportunity for studying the specificities of the changes occurring. *Neurospora* was selected as the organism to study because its life cycle and cultural characteristics make it admirably suited to a genetic analysis of such changes. In this first report our principal aim is to describe the method of approach to the general subject.

INTRODUCTORY CONSIDERATIONS AND METHODS
Growth Curves as Indicators of Adaptive Changes
 The tube method of Ryan, Beadle and Tatum (1943) for the study of growth rates in *Neurospora* is convenient for observing changes in growth rates and in the character of the growth resulting from the response of the organism to the substrate used. In this method tubes of suitable lengths are inoculated at one end, and, as the mycelium advances down the tube, the position of the frontier is marked at convenient intervals. After the growth has reached the far end of the tube, samples can be removed for tests of the persistence of any adaptive changes that have occurred, either by inoculating fresh tubes for a comparison of growth responses with those of untreated material, or by outcrossing to determine if gene changes have occurred.

Normal growth curves The characteristics of the normal growth curve of *Neurospora* (i.e. the wild-type strain on standard medium) are illustrated in curve A of figure 1 (cf. Ryan, *et al.*, 1943, fig. 1).

Ryan *et al.* found that the time required for the germination of conidia (section a of curve A) varied with the age and condition of the conidia, and we have observed variation depending upon the size of the inoculum. After germination there is a stage (section b) characterized by an increasing growth rate which ends in a stage (section c) in which the rate remains constant to the end of the tube. The preliminary lag phase is believed by Ryan *et al.* to be governed by the time necessary to build up a steady state of assimilation and an optimal density of hyphae at the frontier. They found that this lag phase could be greatly shortened if mycelial mats were used as inocula.

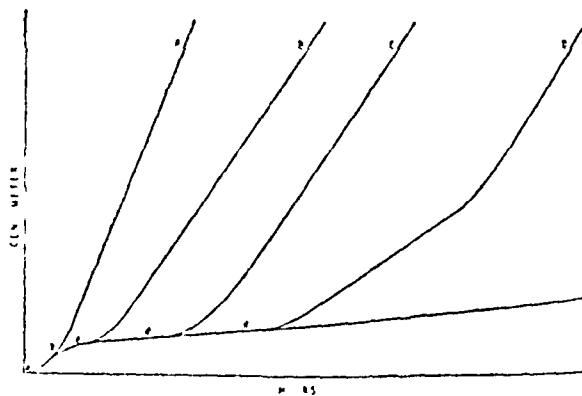


Fig. 1 Types of growth curves. A, normal curve, B to D, adaptive curves, a, germination, b, period of increasing growth rate, c, period of constant growth rate, d, second lag phase.

Adaptive growth curves When grown on certain media *Neurospora* characteristically exhibits a different sort of growth curve, the important feature of which is a second lag phase (section d of curves B, C and D in figure 1, cf. figure 3) intervening before the final steady rate (section c of the same curves) is attained. We interpret such curves to indicate that, by the end of the second lag phase, the organism has become adapted to the substrate, but the universal validity of this interpretation is certainly open to question.

In certain instances there is independent evidence that an adaptive mechanism has been at work without resulting in this adaptive type of growth curve. For example, lactase and inulase are adaptive enzymes, produced only in response to specific substrates, yet the growth curves on lactose and inulin (figure 2) are not essentially different from the normal curve. On the other hand, mutant strain #E-1095, obtained from antiserum treatment (Emerson, 1944), when grown on solid medium at 35°, produced typically adaptive-type growth curves when grown on maltose, and typically normal curves on dextrose (figure 3), and yet when grown in liquid culture at

the same temperature, maltase is secreted into the medium regardless of the carbon source present. In this instance, if the growth curve indicates an adaptive change, it is not due to the adaptive formation of maltase, unless (as is known to be the case in some instances) the response of this strain is completely different on liquid and on

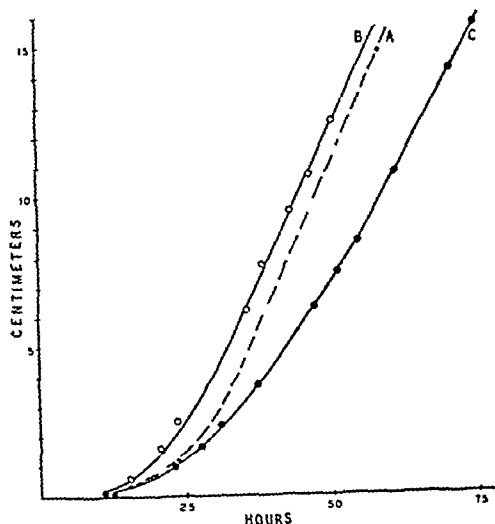


Fig 2 Growth curves of wild type (#1A) on different carbohydrates at 28° A, 2% dextrose, B, 2% inulin, C, 2% lactose

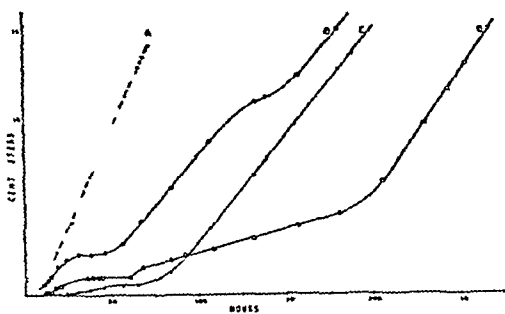


Fig 3 Growth curves of mutant strain #E-1095 on 2% dextrose (A), and on 2% maltose (B, C and D) at 35°

solid media. Even with the occurrence of such "exceptional" responses as those just described, we believe that the shape of the growth curve must frequently reflect adaptive changes. Support for this view is to be had from studies with sulfonamides to be reported below.

Morphological appearance of growth. During the second lag phase (figures 1 and 3) growth does not occur uniformly, instead there are sudden advances of a "feathery" growth (figure 4, A) fol-

lowed by periods in which no linear growth occurs, but in which the growth becomes heavier (figure 4, B). When adaptation occurs the feathery growth changes to form a typical frontier (figure 4, D) of numerous, roughly parallel hyphae, as described by Ryan *et al* (1 c).

Persistence of Adaptive Changes. Adaptive changes as inferred from growth curves may be of almost any degree of permanence. Conidia, or mycelium, taken from the end of a tube showing adaptation, and inoculated into fresh tubes may result in growth in which the second lag phase is lacking, indicating that adaptation persists through such transfers. In other examples of adaptation, the second lag phase in the fresh tube may be shortened, in still others it may be of as great duration as from inocula from non adapted

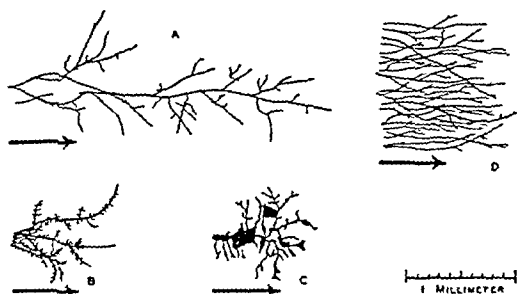


Fig 4 Camera lucida drawings of portions of mycelial frontiers A, feathery growth, B, retarded growth, C, inhibited growth, D, adaptive growth, beginning of formation of uniform frontier. Arrows indicate direction of growth

material, in which case the adaptation has not persisted through the transfer.³ Again, some adaptive changes are accompanied by gene mutation whereas others are presumably not (see discussion under "stability of mutations" below). Responses of each of the types just discussed have been observed in the experiments reported below.

Genetic analyses. The genetic method of testing for mutation in *Neurospora* has been outlined in many papers from the Stanford laboratories, *e.g.*, Beadle and Tatum (1941, 1945), Regnery (1944), etc., while a more general treatment of genetic methods for this material is to be found in Linde-

³ When mycelium is used in inoculations, small pieces of agar, generally not more than 3 mm square, and containing the hyphal tips are transferred to the fresh tubes. It is probable that the shock of cutting close to the growing tips throws them into a resting condition. That adaptive changes would persist without such injury is evident from the steady growth rate obtained in tubes of greater length.

gren (1942) and Beadle (1945) The genetic features essential to this study may be briefly summarized

There are two mating types, designated A and a Sexual reproduction always involves a mating between those two types Both mating types are self sterile and can be considered as hermaphroditic since each is capable of forming properithecia (i.e., the primordia of the fruiting bodies), and each can serve as the fertilizing parent Backus (1939) has shown that (in *Neurospora sitophila*) trichogynes from the properithecia fuse with conidia, or mycelium, of the fertilizing parent, and that nuclei from the conidia migrate down the trichogynes into the properithecia In the developing perithecium many ascogenous cells are formed, in each of which there are two nuclei, one descended from the properithecial parent, the other from the fertilizing parent The two nuclei fuse to give the only diploid nucleus occurring during the life cycle This fusion nucleus, or fertilized egg, immediately undergoes the two reduction divisions (meiosis) in which the genes contributed by the two parents are assorted among the four resulting nuclei Each of these four nuclei undergoes an additional mitosis, so that each genotype produced in meiosis is represented by duplicate spores in the ascus Since all three division figures are oriented lengthwise in the ascus, and do not overlap, the positions of the resulting spores faithfully indicate the relationships between them (cf figure 8, p 386) By culturing all eight spores from an ascus, one obtains a complete picture of the genes contributed by both parents If a particular variant represents a gene mutation, it should be recovered from four spores in each ascus produced by mating the variant to wild type

Since *Neurospora* is a coenocyte, having many nuclei in a common cytoplasm, it is possible to have mixtures of genetically different nuclei in a single hypha or conidium A detailed description of the behavior of artificially produced heterocaryons has been published by Beadle and Conradt (1944) When adaptive changes are a result of mutatron, it is likely that only a portion of the nuclei will carry the mutated gene, the remainder retaining the original, wild-type allele To test for such mixtures, conidia of the adapted strain are spread over properithecia of a normal strain of the opposite mating type Since each properithecium picks up nuclei from a different conidium, a large number of nuclei from the adapted parent may be tested by isolating spores from one ascus per perithecium

Stability of mutations We generally think of genes as being very stable, and suppose that once they have mutated they will be stable in the mutated condition This is not necessarily true, as may be illustrated by an example of a mutant

that reverted to wild type so rapidly that it could not be preserved Mutant strain #L-1905a, obtained from antiserum treatment (Emerson, 1914), was immediately subcultured on various media Regardless of the medium used, the cultures produced either almost no growth, or very abundant growth Material from cultures of each

TABL 1
Genetic tests of reversion to wild type of mutant strain #E 195a
Frequencies of wild type and mutants in outcrosses to wild type #1A Each line represents the progeny of one ascus

	MUTANTS			WILD TYPE
	Mating type			
	A	a	?	
Variant culture 1	—	3	—	—
	—	3	—	4
	—	2	—	4
	—	1	—	2
Variant culture 2	—	—	—	1
	—	—	1	—
	—	—	—	3
	—	—	—	5
	—	1	—	4
	—	—	—	3
Variant culture 3	—	—	—	2
	—	—	1	2
	—	2	—	1
	—	—	—	4
	—	2	—	3
Variant culture 4	—	1	—	4
	—	1	—	1
Reverted culture 1	—	—	—	1
	—	—	—	1
	—	—	—	6
	—	—	—	6
Reverted culture 2	—	—	—	7
	—	—	—	2
	—	—	—	4
Reverted culture 3	—	—	—	1
	—	—	—	6
	—	—	—	3
Reverted culture 4	—	—	—	2
	—	—	—	7
	—	—	—	4
Reverted culture 5	—	—	—	4

type was used in crosses to wild type, with the results shown in table 1 Crosses from cultures with the poor type of growth in each instance reproduced this type in most asci In one ascus there were more than four wild-type spores, indicating a reverse mutation Each mutant type tested proved to be of mating type a, indicating close linkage between the mutant gene and the "sex" locus Crosses from rapidly growing cul-

tures yielded no mutant types even in the five asci from which more than four spores germinated, indicating that there had been back-mutation to wild type associated with reversion to the normal type of growth

In this example it was shown that a mutation had occurred, yet the mutant gene reverted so rapidly that the mutant form could not be maintained in stock. It is possible that some adaptations are accompanied by gene mutations to still less stable forms. By analogy to conditions favoring enzyme stability, it is possible that some mutations might persist only in the presence of the specific substrate. Adaptations accompanied by mutation of this sort would ordinarily be considered non-genetic

carrying genes close to the centromeres of different chromosomes were kindly supplied by Professor G W Beadle of Stanford University

EXPERIMENTAL Adaptation to Sulfanilamide
When grown on sulfanilamide at concentrations greater than 10^{-3} moles per liter, *Neurospora* exhibits the adaptive type of growth curve discussed earlier (see curves of controls, C in figures 5 and 6). Transfers from tubes showing adapted growth generally respond exactly as do transfers from untreated material. There is no indication of persistence of adaptation through such transfers (see footnote 3, p 373)

Wild-type strain #E-5297a was grown in liquid culture for three transfers in the presence of sulfanilamide in concentrations of 1/172, 1/130

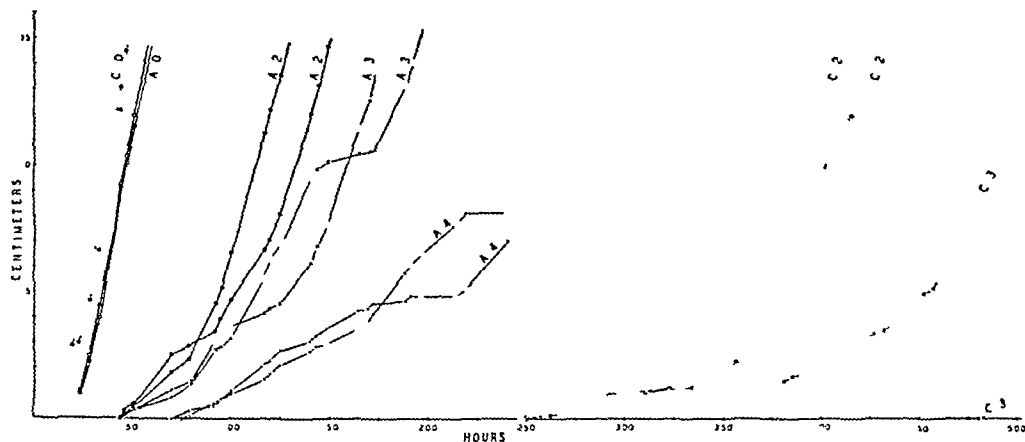


Fig 5 Growth curves of adapted (A) and control (C) cultures on varied concentrations of sulfanilamide at 28° A-O and C-O, no sulfanilamide, A-2 and C-2, 1/172 moles per liter, A-3 and C-3, 1/130 moles per liter, A-4, 1/86 moles per liter, control culture failed to grow at this concentration. Inocula dry conidia

Material The wild-type stocks used in the experiments with sulfonamides are strains #E-5256A and #E-5297a of *N. crassa*. These were derived from crosses between wild-type strains Abb-4A and #25a, and #1A and Abb-12a respectively.⁴ The new wild-type strains eliminated a gene carried by the Abbott strains which, when present in both parents, leads to ascospore abortion, and a gene carried by #1A and #25a which prevents growth on lactose and inulin at 35° (mutant strain #E-1095, referred to above, is due to an allele of this gene). In developing the new wild-type strains, selection was also made for a high degree of fertility and ascospore viability on intercrossing. For use in linkage tests, stocks

and 1/172 moles per liter, respectively, and then tested for sulfanilamide resistance in growth tubes. The length of the second lag phase was considerably reduced over that observed with untreated material. A second series of growth tubes was inoculated with conidia produced after growth through a tube containing 1/172 moles per liter of sulfanilamide, with the results shown in curves A-2, A-3 and A-4 in figure 5. Persistent adaptation is shown by the shortened lag period at low sulfanilamide concentrations, by increased final growth rates at intermediate concentrations, and by growth at higher concentrations than were tolerated by untreated material (C curves in figure 5).

Inocula from the ends of the tubes represented by curves A-O and C-O in figure 5 duplicated these results, indicating that the adaptation persists through at least one transfer in the absence of sulfanilamide. Conidia from the end of one of the

⁴ Strains are numbered as in Beadle and Tatum (1945) for those developed at Stanford University. Strain numbers preceded by an E- are Emerson's numbers, that by a C- is Cushing's

cating that the degree of resistance is influenced by modifying genes. In the presence of the gene inhibiting growth on lactose and inulin at 35° (carried by wild-type strains #1A and #12a) the

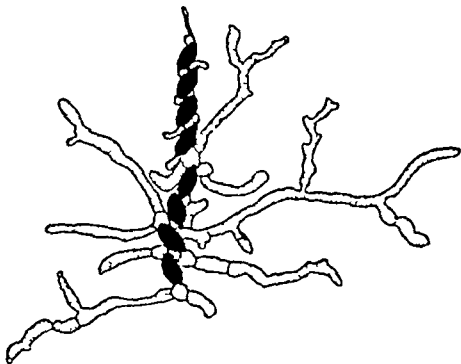


Fig 8 Camera lucida drawing of germinating ascospores. An entire ascus was transferred to agar containing 1/43 moles per liter sulfanilamide, and heated to induce germination. Four wild-type spores at one end of the ascus produced short germ tubes before growth was inhibited by sulfanilamide, the four spores at the opposite end of the ascus, carrying the sulfanilamide-tolerant gene, produced hyphae which were not inhibited by sulfanilamide. This distribution of spores within the ascus indicates that the mutant gene segregated at the first meiotic division.

TABLE 3

Numbers of asci with different arrangements of spores in crosses between the sulfanilamide-tolerant strain and different linkage testers

Legend: s, sulfanilamide tolerant, m, linkage tester; +, wild type, ms, sulfanilamide tolerant and linkage-tester genes carried in same spore (ms and + represent recombinations between genes from the two parents)

CROSS		SEGREGATION			
Sulfa strain	Linkage tester	1st div s 1st div m		1st div s 2nd div m	2nd div s 1st div m
		4m 4s	4ms 4+	2m 2+ 2ms 2s	2m 2ms 2+ 2s
		4m 4s	4ms 4+	2m 2+ 2ms 2s	2m 2ms 2+ 2s
E-8622a	16117(3825-5)A	7	3	1	1
E-8622a	44101(1484 1)A	3	10	1	0
E-8622a	51602(4345 2)A	6	0	0	0
C-40a	51602(4345 2)A	8	0	0	0
Expected frequencies					
Independent genes		50%—	50%—	0%+	0%+
Linked genes		100%—	0	0%+	0%+

sulfanilamide-tolerant mutant produces very little growth under any conditions.

Reversion to wild type. In figure 7, and in table 4, certain cultures have been marked as having "reverted." The reversions consist in a simultaneous change in growth habit, from the surface-growth of the mutant to the more lush growth of wild type, and in growth rate to a rate frequently

approximating that of wild type under similar conditions, and considerably greater than the normal optimal growth rate of the mutant. These reversions have occurred in only those growth tubes in which the concentration of either sulfa-thiazole or p aminobenzoic acid was high enough.

TABLE 4

Growth rates, millimeters per hour, of segregants carrying the sulfanilamide tolerant gene. Inoculations from freshly isolated ascospore cultures. The first four isolates are from one ascus and are numbered in order.

ISOLATE	AGE IN DAYS OF ASCO SPORE CULTURE	CONCENTRATION, MOLES PER LITER					
		0	Sulfanilamide			Sulfathiazole	p amino- benzoic acid
			1/160	1/80	1/40	1/160	1/320
E 11132	9	2.8	—	—	1.2	0.2	3.6*
		2.7	—	—	0.2	0.2	2.7*
	15	2.4	2.5	1.7	1.3	—	—
		2.5	2.6	1.6	1.4	—	—
E 11133	9	2.6	—	—	0.8	0.2	0.1
		2.6	—	—	1.0	0.2	0.1
	15	2.4	2.5	1.5	1.6	—	—
		2.4	2.7	1.6	1.4	—	—
E 11134	9	2.0	—	—	1.0	0.2	0.1
		2.0	—	—	1.0	0.2	0.1
	15	2.1	2.0	1.4	1.4	—	—
		1.9	1.9	1.4	1.0	—	—
E 11135	9	2.0	—	—	0.9	0.2	0.1
		2.0	—	—	2.0	0.3	0.1
	15	2.4	2.2	1.3	1.2	—	—
		2.2	2.2	1.5	0.7	—	—
E-11145	9	2.0	—	—	0.2	0.1	2.6*
		2.0	—	—	2.1	4.2*	0.5
	15	2.4	2.2	1.3	1.4	—	—
		2.2	2.2	1.5	1.2	—	—
E 12890	9	2.2	—	—	1.0	0.2	3.6*
		2.2	—	—	2.3	3.6*	0.1
	15	2.3	2.2	2.2	2.2	—	—
		2.1	2.2	2.4	2.2	—	—

* Reverted growth, resembling wild type in growth habit and growth rate.

to markedly depress the growth rate. They have not occurred in the absence of p-aminobenzoic acid and sulfonamides, a condition which also favors wild-type nuclei when present (cross #4, table 2).

In outcrosses of such reverted cultures to wild type, reverse mutation is suggested in two instances in which germination was obtained from complete asci, one from an outcross of one reverted culture (#E-11132 with growth rate 3.6 mm/hr on

p aminobenzoic acid, table 4), and eight complete asci from another (#E-11145 with growth rate 4.2 mm/hr on sulfathiazole, table 4). Wild-type cultures, as judged by growth habit, were obtained from all eight spores of each of these nine asci, indicating that in these instances, reversion was accompanied by mutation. The data are insufficient to indicate whether the mutation to wild phenotype involved the sulfanilamide-tolerant gene itself, or some other gene.

A Sulfanilamide-Requiring Strain From crosses of the sulfanilamide-tolerant strain to wild type, we have in several instances obtained segregants which, along with tolerance to sulfanilamide, showed poor growth on other media. Only one of these has been tested for growth requirements, strain #E-13190 (and its twin, #E-13189). This strain makes little or no growth in the absence of sulfonamides, or in the presence of p aminobenzoic acid of 10^{-2} to 10^{-5} moles per liter. Optimal growth on sulfanilamide and on sulfapyridine occurs in concentrations of about 0.02 moles per liter, and on sulfathiazole at higher dilutions (figure 9). Preliminary genetic tests indicate that the change to the condition requiring sulfonamides for growth involves mutation at a locus distinct from the sulfanilamide-tolerant gene.

Discussion The experimental results reported above, while not going very far towards accomplishing the aims set out in the introductory paragraphs, do constitute a survey of the suitability of our material to such a study. Aside from pointing out promising lines of investigation, some of the observations are not without interest of their own.

Physiological Processes Concerned in Adaptation
Interactions of p-aminobenzoic acid and sulfonamides The general features of the antagonistic interactions between p-aminobenzoic acid and the sulfonamides have been extensively discussed in recent reviews (Welch, 1945; Henry, 1944).

In *Neurospora*, Tatum and Beadle (1942) have shown that p aminobenzoic acid is an essential metabolite, normally synthesized by the wild-type organism, that growth is inhibited by sulfanilamide—both in the wild type and in a mutant strain (#1633) which is unable to synthesize p-aminobenzoic acid, and that the inhibitory action of sulfanilamide is antagonized by p-aminobenzoic acid in both strains.

Growth of *Neurospora* is likewise inhibited by p aminobenzoic acid in concentrations comparable to those giving sulfonamide inhibition (figure 7, p 385). In contrast to the p aminobenzoic acid antagonism of sulfonamide inhibition (cf figure 10A), the inhibition of growth in wild type by p aminobenzoic acid is not antagonized by sulfanilamide (figure 10B). This observation makes it seem unlikely that the failure of strain #E 13190

to grow in the absence of sulfonamides can be due to an over production of p-aminobenzoic acid to an extent which inhibits growth except in the presence of an antagonist, such as sulfanilamide. The

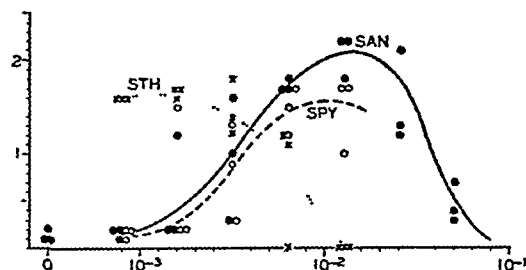


Fig 9 Growth rates, millimeters per hour, of the sulfonamide-requiring strain (#E-13190) on varied concentrations, moles per liter, of different sulfonamides: STH, sulfathiazole; SAN, sulfanilamide; SPY, sulfapyridine. Inoculation by mycelial transfer, temperature 34° .

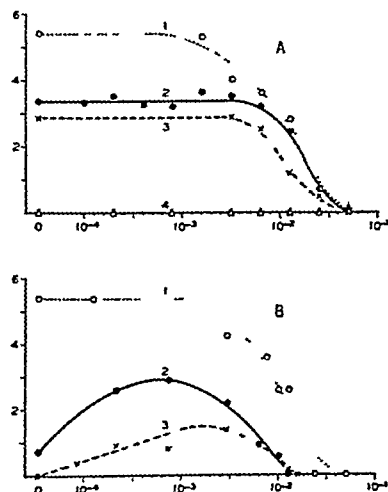


Fig 10 A, growth rates, millimeters per hour, of wild type (#E-5256A) on increasing concentrations, moles per liter, of sulfanilamide, curve 1, in absence of p aminobenzoic acid, curves 2, 3 and 4, in the presence of 1/120, 1/100 and 1/80 moles per liter of p aminobenzoic acid, respectively. B, growth rates on increasing concentrations of p aminobenzoic acid, curve 1, in the absence of sulfanilamide, curves 2 and 3, in the presence of 1/40 and 1/20 moles per liter of sulfanilamide, respectively.

uncertainty on this point arises from the possibility that, in the genetic background of strain #E-13190, sulfanilamide may antagonize the fungistatic action of p aminobenzoic acid.

It is still more improbable that strain #C-40 owes its tolerance to sulfanilamide to an increased production of p aminobenzoic acid, such as has

been reported in *Staphylococcus* (Landy, *et al.*, 1943). If this were true, the mutant strain should be more resistant than wild type to sulfathiazole, as well as to sulfanilamide (*cf.* figure 7). Furthermore it would not be expected that sulfathiazole inhibition would be antagonized by relatively small additional amounts of p-aminobenzoic acid, such as shown in figure 7D. Direct tests have yet to be made on the amounts of p-aminobenzoic acid produced by strains #C-40 and #E-13190 when grown in the presence of sulfanilamide.

Physiological rôle of p-aminobenzoic acid and sulfanilamide Giese and Tatum (1946) found that p-aminobenzoic acid acted as a respiratory stimulant in strain #1633 (which is unable to synthesize p-aminobenzoic acid) of *Neurospora* when added after the culture had been starved for p-aminobenzoic acid. The same authors (Tatum and Giese, 1946) were unable to find any inhibition of respiration, either in mutant strain #1633 or in wild type, following the addition of sulfonamide. Aside from these studies, nothing is known of the physiological rôle of p-aminobenzoic acid in *Neurospora*, nor of sulfonamides in growth inhibition. The two new strains, #C-40, which is tolerant to sulfanilamide, and #E-13190, which requires sulfonamide for growth, offer the possibility of studying these questions more expeditiously.

Cytoplasmic vs Genetic Adaptation A distinction has long been made (Karstrom, 1938, Yudkin, 1938) between adaptation in the restricted sense, involving the production of an enzyme in direct response to the substrate without gene change, and the occurrence of spontaneous mutations, which is not directly influenced by the substrate, although, once having occurred such mutations are given a selective advantage by the substrate. The former may be considered to be a direct cytoplasmic response to the substrate, the latter to accidental gene changes. It has been suggested (Emerson, 1945) that the mechanism by which cytoplasmic adaptation is induced might also serve as a means of inducing a corresponding specific mutation.

Stepwise production of sulfanilamide tolerance In most organisms, complete resistance to sulfonamides does not arise all at once, but by successive stages of increased resistance (*cf.* Henry, 1944, for review). The development of sulfanilamide tolerance in *Neurospora* apparently involves three steps. (1) At concentrations of sulfanilamide permitting some growth, the shapes of the growth curves suggest that wild-type strains invariably develop some tolerance to sulfanilamide which, however, is extremely transient, being lost whenever active growth stops, as in conidial formation, or when the hyphal branches have been cut close to their tips. (2) The first persistent adaptation (figure 5, p. 383) appeared after longer treatment

with sulfanilamide and apparently involved no gene change (cross #1 in table 2). (3) The more fully adapted strain (figure 6, p. 384), appearing after still further treatment, was accompanied by gene mutation (crosses #2 and #3 in table 2). A comparison of crosses #3 (table 2), from material that had grown down a tube with a high concentration of sulfanilamide, with cross #1, from material grown in the absence of sulfanilamide, indicates that the sulfanilamide medium selects for mutant nuclei, control medium for wild type nuclei. Had the first persistent adaptation involved gene mutation of the sort found later, we should have expected to recover some mutant forms from cross #1, and we should not have expected the adaptation to persist unaltered through a transfer in the absence of sulfonamide, where there is selection against the mutant, but the data are too few to make this point certain.

At present we do not know that there is any relationship between these different grades of sulfanilamide tolerance. Once the physiological changes accompanying full adaptation have been determined, it should be possible to tell if the same physiological responses appear in the more transient adaptation.

Directed mutation While the number of investigations designed to test specifically directed mutation is small, there are no well authenticated cases known in sexually reproducing forms (*cf.* Beadle, 1945, for review), unless the case of one gene specifically inducing mutation in another (Rhoades, 1938) is considered to be of this sort. In asexual forms, the only demonstrated case is that of type-transformation in pneumococcus (*cf.* Dubos, 1945, for review).

The mutation to sulfanilamide tolerance (resulting in strain #C-40) occurred under conditions which would select for spontaneous mutations of that sort, making it difficult to recognize directed mutations should they occur. Reversions of mutant strain #C-40 to wild type, however, should be amenable to studies of this sort. It is possible to set up two conditions, both of which select for wild-type nuclei, but with reversions occurring in only one of them. On medium containing neither sulfonamides nor p-aminobenzoic acid, wild-type nuclei are favored over mutant nuclei (*cf.* cross #3 and cross #4, table 2), yet reversions have not been observed under these conditions. At concentrations of p-aminobenzoic acid sufficient to depress the growth rate of #C-40, reversions are very frequent. By the use of artificially constructed heterocaryons it is possible to measure the selective pressures quite exactly under the two sets of conditions, and thus determine whether or not the reverse mutations are specifically induced by the treatment. Studies of

this sort have not yet progressed far enough to be meaningful

Acknowledgments We wish to express our thanks to Edna Herrmann, Helen Arnerich, Hermione Grant, Mary R. Emerson, and Dorothy Cone for assistance during different phases of the experiments reported. We have received helpful criticism from many colleagues, to whom we express our gratitude without listing them all by name.

SUMMARY The use of the tube method of Ryan, Beadle and Tatum (1943) for the study of adaptive changes in *Neurospora* is described. A mutant strain, # C-40, obtained following growth on sulfa-

nilamide, is completely resistant to sulfanilamide and sulfapyridine, has an enhanced tolerance to sulfacetamide, but is more susceptible to sulfathiazole and to p-aminobenzoic acid than the wild-type strain. Growth inhibition by sulfathiazole in the mutant strain is counteracted by low concentrations of p-aminobenzoic acid. The mutant strain reverts to wild type in the presence of either p-aminobenzoic acid or sulfathiazole, but seldom, if ever, in their absence. A further mutation resulted in a strain which requires sulfonamides for growth, and which is not able to grow by any concentration of p-aminobenzoic acid tested.

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SYMPOSIUM ON BIOCHEMISTRY OF MALARIAL PARASITES

INTRODUCTION

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The following papers report part of the investigations conducted during the war by a group organized by the Panel on Biochemistry, Division of Chemistry and Chemical Technology, National Research Council, cooperating with the Board for the Coordination of Malaria Studies. These investigations were conducted under contract with the Office of Scientific Research and Development on behalf of the Committee on Medical Research.

The primary aim of the investigations was to uncover some critical link in the metabolism, or growth requirements, of the parasites which might

provide a lead to the synthesis of an improved antimalarial. This was stated frankly to be a gamble but also, and with particular reference to the probability that malaria will continue to be a disease of major importance, it seemed appropriate, even during the war, to lay certain foundations for a better understanding of the biochemistry of the parasites.

As noted above, the following papers review only a part of the accomplishments, but what is here revealed, I am sure, attests the fact that the effort was well spent.

ENZYME SYSTEMS OPERATING WITHIN THE MALARIAL PARASITE

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Our knowledge of the enzymic composition of the malaria parasite is confined to information regarding a single phase of the life cycle of the parasite—the erythrocytic stage, in which the parasite penetrates and develops within the erythrocyte of its vertebrate host. Biochemical studies of these forms were initiated by Christophers and Fulton in 1938, using the monkey parasite, *P. knowlesi* (1). Since then, studies have been made by numerous investigators using this infection (2, 3, 4), as well as *P. mur* (3), the human parasites, *P. vivax* (5), *P. falciparum* (5), *P. malariae* (5), the duck parasite *P. lophurae* (6, 7), the chicken parasite *P. gallinaceum* (8), and the canary parasite *P. cathe-merium* (9). With some of these species, our information is very meager, but no one has yet observed any striking qualitative dissimilarity of a chemical nature between the various species of *Plasmodia*. It is not yet possible to offer any biochemical explanation of the species specificity of the various infections.

In no single case has a pure enzyme been isolated from the protoplasm of the malaria parasite, and it is necessary therefore to describe the enzymic composition of the parasite in terms of the metabolic reactions carried out by the parasites.

There are three types of parasite preparations available for investigation. First, it is possible to study the metabolic and enzymic characteristics

of saline suspensions or buffered saline suspensions of parasitized erythrocytes. Ball and his associates (4) have devised techniques for the *in vitro* cultivation of suspensions of parasitized erythrocytes so that long periods of observation are possible. In experiments with parasitized erythrocytes, it is necessary to run controls using normal erythrocytes. However, since the metabolic activity of the normal erythrocyte is much lower than that of the parasitized erythrocyte, there is usually no question of the relation between the particular enzymic activity observed and the parasite itself.

Second, it is possible to study the metabolism and enzymic properties of parasites liberated from the erythrocyte. This was first done by Christophers and Fulton (10) using saponin as the lytic agent. Hellerman and his associates (7) by carefully controlling the quantity and time of incubation with saponin, have been able to obtain erythrocyte-free parasite preparations without appreciably altering the metabolic properties of the parasites. In our laboratory (11) we have used erythrocyte-free suspensions of *P. gallinaceum* prepared by the use of specific hemolytic antiserum obtained by injecting normal erythrocytes of the chicken host into rabbits. Parasites prepared by this technique are completely free from erythrocytes, stain normally with Giesma stain, and possess high metabolic activity.

Finally, it is possible to work with cell-free extracts prepared from these various parasite materials. Under properly controlled conditions some enzymic reactions have been studied in distilled water hemolysates of parasitized erythrocytes (12). In other cases, extracts have been prepared from free parasites which have been liberated from erythrocytes by the use either of saponin or of water (12).

I should like to describe first our knowledge of the enzyme systems involved in the utilization of molecular oxygen and of proteins and simpler nitrogenous substances by the parasite, and then proceed to a discussion of the carbohydrate metabolism of the parasite, of which our knowledge is more detailed.

Cyanide inhibits the oxygen uptake of erythrocytes parasitized with various species of the *Plasmodia*, as well as that of the free parasites themselves (1, 2, 4, 7, 9, 13). Diethylthiocarbamate and carbon monoxide inhibit the oxygen utilization of *P. knowlesi* (5), and sodium azide inhibits the respiration of *P. gallinaceum* (13). These facts suggest that the heavy metal catalysts of the Warburg-Keilin cytochrome system are involved in the respiratory mechanism of the parasite, but direct evidence to this point is lacking. The presence of flavoproteins is suggested by the finding of Ball and his associates (4) that erythrocytes parasitized with *P. knowlesi* contain flavin adenine dinucleotide. Work in our laboratory, with cell-free extracts and free parasites, has demonstrated the existence of several dehydrogenase systems requiring DPN and TPN (12).

Changes in composition of parasitized erythrocytes during the growth of parasites *in vitro* show that the parasite is capable of the synthesis and metabolic transformation of cholesterol, and phospholipids.

Some information is also available concerning the enzyme systems involved in the nitrogen metabolism of the erythrocytic forms of the malaria parasite. It is clear that the nitrogen necessary for the synthesis of parasitic protoplasm *in vivo* must be derived either from the amino acids or other small nitrogenous fragments present in the blood serum or by the breakdown of the intracellular protein of the erythrocyte. There is evidence that both reactions may occur. Ball and his associates (4) have shown in their cultivation experiments that amino acids, purines, and pyrimidines are necessary for good growth and reproduction of the malaria parasite. Likewise, evidence demonstrating that intracellular protein can be hydrolyzed is available from *in vitro* experiments in which extracellular nitrogen has been entirely excluded. While this may not apply to the early experiments of Christophers and Fulton (1), in which the formation of amino nitrogen from

intracellular protein was inferred from experiments in which serum was used as part of the suspending medium, it is undoubtedly true of more recent experiments both with *P. knowlesi* and *P. gallinaceum*. In the first case, Wendel (2) has shown that ammonia is formed in the absence of glucose by suspensions of parasitized erythrocytes. A similar process in *P. gallinaceum* has also been studied in our laboratory (14).

When suspensions of erythrocytes parasitized with *P. gallinaceum* are incubated under the conditions shown (table I), a considerable formation of amino nitrogen takes place. If glucose is excluded from the medium, appreciable quantities of ammonia are formed. It will be seen that the total amount of amino nitrogen plus ammonia formed under these conditions remains approximately the same in the absence or presence of

TABLE I

Effect of glucose on the nitrogen metabolism of parasitized erythrocyte suspensions

Parasitized erythrocytes were washed and suspended in Ca-free phosphate saline to which no glucose had been added. In the samples which were incubated without glucose the glucose solution was replaced by an equal volume of Ca-free phosphate-saline. Air 40, 4 hours. Values are given as micromoles per cc erythrocytes.

	0.01 M GLUCOSE ADDED	AMINO NITROGEN FORMED	AMMONIA NITROGEN FORMED	AMINO NITROGEN PLUS AMMONIA NITROGEN FORMED	OXYGEN USED
Expt 1					
+		33.3	7.7	41.0	153
-		23.0	20.0	43.0	76
Expt 2					
+		23.3	1.4	24.7	109
-		15.8	8.4	24.2	53

glucose, but larger quantities of ammonia are formed in the absence of glucose. It seems possible that in the absence of glucose, some of the liberated amino acids are deaminated. A relationship between oxidative processes and the formation of amino nitrogen by the parasite is indicated by observations that amino nitrogen formation is greatly depressed under anaerobic conditions and that amino nitrogen formation is significantly decreased by low concentrations of quinine and atabrine (14), substances known to inhibit the respiration of the malaria parasite. It is possible to prepare cell-free extracts from *P. gallinaceum* which contain active proteinases. As shown in table II, these extracts will hydrolyze hemoglobin at a slow rate but will hydrolyze acid-denatured hemoglobin with considerable speed. The proteolytic activity of these cell-free extracts is not affected by the oxygen tension, nor is it inhibited by concentrations of quinine and atabrine which

decrease the formation of amino nitrogen in intact parasitized erythrocytes (14). It follows therefore that the apparent coupling between amino nitrogen formation and oxidative activity in the parasitized erythrocyte is not directly concerned with the proteinases themselves but with other, as yet unknown, properties of the metabolic systems involved.

It is not certain that the intracellular protein broken down under these circumstances is entirely hemoglobin although the appearance of free hemeatin (15, 16) in the parasitized erythrocyte is presumably accompanied by the release of the globin portion of the hemoglobin for utilization by the parasite. We have failed to observe any significant decrease in hemoglobin during the formation of appreciable quantities of amino nitrogen by the

TABLE II

The proteinase activity of cell free extracts of the malaria parasite

1.0 cc. cell free extract and 0.25 cc. 0.1 M phosphate, pH 6.5, were incubated 2 hours at 40°. Hemoglobin and globin were added in amounts of 200 micromoles total nitrogen. Values are expressed as micromoles of amino nitrogen per cc. extract and represent the average of 5 experiments.

AMINO NITROGEN	SUBSTRATES ADDED		
	None	Native horse hemoglobin	Denatured horse globin
	(1)	(2)	(3)
Initial	0.66	0.66	0.85
Final	1.02	1.41	7.16
Increase	0.37	0.75	6.31

malaria parasite (16). However, the expected changes would be very small and might possibly escape detection.

Ball and his coworkers (4) have shown an increase in nucleic acid phosphorus during the *in vitro* growth of the parasite. Miller and Kozloff (17), using material prepared by the saponin technique, have shown that both normal and parasitized chicken red cells possess enzymes which are capable of the depolymerization of ribose nucleic acid. In parasitized cells, the reaction occurs twice as fast as in normal cells and proceeds to the further stage in which significant quantities of inorganic phosphate are liberated. The process is not inhibited by quinine or atabrine.

In summary, then, one can say that our limited knowledge of the nitrogen metabolism of the parasite involves a picture in which the organism engages in an active hydrolysis and metabolism of intracellular protein, this process being linked, in some fashion, with the oxidative metabolism of the parasite.

In regard to the carbohydrate metabolism of the malaria parasite, it has been known since the ex-

periments of Christophers and Fulton (1) that glucose can be oxidized to carbon dioxide and water by the parasite. Fructose, mannose, maltose, glycerol, glycerophosphate, pyruvate and lactate are all utilized when added to suspensions of erythrocytes parasitized by various species of *Plasmodia*. The conversion of glucose to lactic acid by *P. knowlesi* was first reported by Wendel (2), and occurs also in *P. gallinaceum* and in other species. Ball and his collaborators (1) have demonstrated the conversion of glycerol into pyruvate during the growth of *P. knowlesi* in monkey erythrocytes. With erythrocyte free suspensions of parasite material, an oxidative utilization of oxalacetate, *cis*-aconitate, α ketoglutarate, succinate, malate, and fumarate can be demonstrated (11, 7).

Perhaps the most complete survey of the intermediate steps involved in the utilization of glucose has been made with *P. gallinaceum* (8, 12, 11). Under anaerobic conditions, glucose is converted quantitatively into lactic acid. In the presence of oxygen, the lactic acid formed from glucose is oxidized to carbon dioxide and water. The rate of formation of lactic acid from glucose is so rapid that lactic acid accumulates even under aerobic conditions. We have shown that the mechanism of lactic acid formation from glucose in *P. gallinaceum* is very similar to the phosphorylating glycolysis occurring in mammalian muscle, yeast, and many other organisms (12).

In extracts of yeast and some animal tissues, glucose is converted into glucose 6-phosphate by ATP in the presence of the enzyme hexokinase. Since the transfer of phosphate from ATP to glucose results in the formation of acid, the reaction can be studied by the Warburg manometric technique in a bicarbonate buffer. In cell-free parasite extracts to which fluoride has been added to prevent the breakdown of ATP by adenosine triphosphatase, there occurs a similar reaction, which comes to a stop when one of the labile phosphate groups of ATP has been transferred to glucose (table III). These manometric data are confirmed by chemical determinations which indicate that the labile phosphate groups of ATP disappear without giving rise to inorganic phosphate and that fructose-1,6-diphosphate is formed. Hexokinase activity is present in both normal and parasitized cells but the greater activity (some 4-5 times) of the extracts from parasitized cells indicate that the hexokinase is a constituent of the parasite.

The phosphorylating glycolysis of muscle extracts also involves a characteristic oxidation in which 3-phosphoglyceraldehyde is oxidized to 3-phosphoglyceric acid in the presence of diphosphopyridine nucleotide, and inorganic phosphate. The 1,3-diphosphoglyceric acid which is formed as an intermediate transfers phosphate to

ADP The necessary ADP may be formed from ATP as the result of hydrolysis by the enzyme adenosine triphosphatase, or by the transfer of one phosphate group to a phosphate acceptor such as glucose or creatine. Magnesium is required as a cofactor for all these phosphate transfer reactions. It can be seen that to study the coupled oxidation of 3-phosphoglyceraldehyde a system must be used which contains catalytic amounts of DPN, ADP (or ATP), and magnesium ions, stoichiometric amounts of 3-phosphoglyceraldehyde, inorganic phosphate, glucose, and pyruvic acid (for the re-oxidation of the reduced DPN), and the appropriate enzymes. The over-all reaction occurring

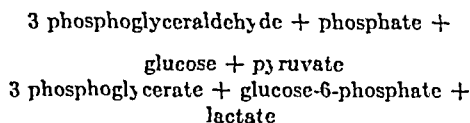
TABLE III

Adenosinetriphosphatase and hexokinase activity in red cell hemolysates

Samples contained 0.028 M NaHCO₃, 0.004 M MgSO₄, 0.0028 M KF, 0.012 M glucose (none when adenosinetriphosphatase activity was being measured), 0.0036 M adenosinetriphosphate (tipped in from side arm after equilibration) and 1.4 cc of hemolysate of normal chicken red cells (equivalent to about 0.36 cc of cells) or 0.7 cc of hemolysate of parasitized red cells (equivalent to about 0.21 cc of cells), in a total volume of 2.5 cc Warburg manometers gas phase 5 per cent CO₂-95 per cent N₂ temperature 39°. The retention factor (observed CO₂/true CO₂) was about 0.7 for mixtures with hemolysates of normal red cells and 0.85 for mixtures with hemolysates of parasitized red cells. Activities are expressed in microliters of CO₂ evolved per cc of red cells per hour.

NORMAL RED CELLS			PARASITIZED RED CELLS		
Number of samples	Adenosine triphosphatase	Hexokinase	Number of samples	Adenosine triphosphatase	Hexokinase
6	56 (31-103)	378 (290-591)	12	76 (44-102)	1630 (590-2270)

in such a system may be represented by the equation



It was felt that the demonstration of such an oxidation in parasite material would be strong evidence for the occurrence of a phosphorylating glycolysis in the parasites. Since the oxidation of 3-phosphoglyceraldehyde results in the formation of acid, the process can be followed conveniently by measuring the carbon dioxide liberated from a bicarbonate buffer containing the test system. Extracts prepared from parasites liberated by saponin were used in these experiments and were capable, as shown in preliminary experiments, of enzymically converting fructose 1,6-diphosphate to 3-phosphoglyceraldehyde and dihydroxyacetone phosphate. In the final experiments, then,

fructose-1,6-diphosphate was used as substrate and fluoride was added to inhibit the adenosine triphosphatase present and to prevent the breakdown of 3-phosphoglycerate to pyruvate. The study of this system gave the data in table IV.

Both arsenate and iodoacetate have characteristic effects on the oxidation of 3-phosphoglyceraldehyde wherever this reaction has been demonstrated. Arsenate is believed to replace inorganic phosphate in the reaction giving 1-arseno-3-phospho-glyceric acid as the product of the oxidation, this substance breaks down rapidly and spontaneously to arsenate and 3-phosphoglycerate. Since the phosphate transfer reactions are usually slower than the oxidation itself, addition of arsenate increases the rate of the oxidation.

TABLE IV

Components of the system oxidizing 3-phosphoglyceraldehyde

The complete system contained 0.026 M NaHCO₃, 0.004 M MgSO₄, 0.008 M phosphate pH 7.4, 0.02 M KF, 0.013 M glucose, 0.013 M sodium pyruvate, 0.0007 M adenosine triphosphate, 0.00007 M DPN, 0.0035 M fructose 1,6-diphosphate (tipped in from the side arm), and 1.7 cc of an extract of parasite material (prepared by saponization, 0.9 per cent NaCl without glucose used for all washings) in a total volume of 2.5 cc Warburg manometers gas phase 5 per cent CO₂-95 per cent N₂ temperature 39°.

SAMPLE	RATE
	Microliters of CO ₂ per hour
Complete system	56
Without fructose-1,6-diphosphate	44
Without glucose	42
Without adenosine triphosphate	41
Without phosphate	39
Without MgSO ₄	34
Without DPN	33
Without pyruvate	27

Iodoacetate in low concentrations strongly inhibits the enzyme catalyzing the actual oxidation of 3-phosphoglyceraldehyde. The expected effects of arsenate and iodoacetate can be demonstrated in extracts of parasite material. Addition of 0.0012 M arsenate and omission of phosphate, glucose, and ATP from the system described in table IV markedly accelerated the rate of carbon dioxide evolution, while addition of 0.0012 M iodoacetate to the system containing arsenate caused an inhibition of more than ninety per cent (table V).

The presence in extracts of parasite material of the enzyme lactic dehydrogenase was demonstrated by means of the colorimetric technique described by Haas (18).

The experiments which have been described indicate that the formation of lactic acid from glucose by malaria parasites occurs by the same reactions which have been demonstrated for the phosphorylating glycolysis that occurs in many other organisms and tissues.

It is also possible with the erythrocyte-free forms of *P. gallinaceum* to draw up a tentative scheme for the mechanism of pyruvate oxidation by this species of malaria parasite

In order to avoid complications arising from the impermeability of the erythrocytic membrane to highly-polar substances such as the dicarboxylic acids, much of the work on the mechanism of pyruvate oxidation in *P. gallinaceum* was carried out with erythrocyte-free parasites, and brief mention must be made of the metabolic properties of the free parasites (11) Unlike parasitized erythrocytes, free parasites require certain added substances in order to oxidize pyruvate at a maximal rate Dicarboxylic acids such as α -ketoglutarate and malate greatly increase the rate of oxygen consumption and pyruvate utilization In addition, manganous ions, ATP, DPN, TPN, thiamin,

TABLE V

The effect of arsenate and iodoacetate on the oxidation of 3-phosphoglyceraldehyde

The complete system contained 0.026 M NaHCO₃, 0.004 M MgSO₄, 0.02 M KF, 0.0035 M fructose 1,6-diphosphate, 0.013 M sodium pyruvate, 0.00007 M DPN, 0.008 M phosphate pH 7.4, 0.013 M glucose, 0.0007 M adenosine triphosphate, and 1.7 cc of extract, in a total volume of 2.5 cc The arsenate sample contained 0.0012 M Na HAsO₄ and no phosphate, glucose, or adenosine triphosphate The iodoacetate sample was like the arsenate sample with the addition of 0.0012 M sodium iodoacetate Warburg manometers, gas phase 5 per cent CO₂—95 per cent N₂, temperature 39°

SAMPLE	RATE
	Microliters of CO ₂ per hour
Complete	143
Arsenate	221
Iodoacetate	19

and diphosphothiamin also accelerate the rate of oxygen consumption and pyruvate utilization in free parasites A wide variety of other compounds—cofactors, vitamins, simple nitrogenous compounds, peptones, and proteins—are without effect upon the rate of pyruvate oxidation in these preparations It is not possible, by the addition of any combination of stimulating substances, to restore completely the free parasite to the metabolic activity which it possesses in the erythrocyte A further examination of this problem would seem highly profitable in terms of biochemical understanding of the actual nature of the parasitic relationship between *Plasmodia* and erythrocytes

Both parasitized erythrocytes and free parasites consume oxygen at an appreciable rate in the absence of added substrates The nature of the substances oxidized under these conditions is not known, but they are apparently oxidized by way of the same metabolic pathways as is added pyruvate In the presence of adequate amounts of

the dicarboxylic acids and the other cofactors just mentioned, free parasites oxidize pyruvate, lactate, and glucose at about half the rate observed with an equivalent quantity of parasite material inside the erythrocyte The rate of glycolysis is the same in both types of parasite preparations

Parasitized erythrocytes oxidize 0.01 M pyruvate almost completely to carbon dioxide and water In contrast, free parasites oxidize 0.01 M pyruvate in part to carbon dioxide and water and in part to acetic acid Under anaerobic conditions, pyruvate is not utilized at all Dismutation into lactate and acetate does not occur

The most generally accepted mechanism for the complete oxidation of pyruvate is the tricarboxylic

TABLE VI

Effect of acids on the tricarboxylic acid cycle on the respiration of parasite preparations

Samples contained 0.6 cc parasitized erythrocytes or 1.2 cc free parasites (from different samples of blood) and the substrates indicated below in 0.001 M concentration, in a volume of 3.0 cc 0.01 M MgSO₄ was added to all samples containing *cis* aconitate or citrate Samples with free parasites all contained the cofactor mixture and also 0.00033 M malate when the substrate was pyruvate Gas phase air, temperature 40°, time 60 minutes Values for parasitized erythrocytes are from a single typical experiment, while those for free parasites represent the average of four experiments

SUBSTRATE ADDED	PER CENT INCREASE IN OXYGEN CONSUMPTION OVER LEVEL WITHOUT ADDED SUBSTRATES	
	Parasitized erythrocytes	Free parasites
Pyruvate	111	167
Oxalacetate	51	102
<i>cis</i> Aconitate	0	44
Citrate	0	16
α Ketoglutarate	8	88
Succinate	18	96
Fumarate	16	179
Malate	1	204

acid cycle of Krebs (19), based largely on experiments with minced pigeon breast muscle Using preparations of *P. gallinaceum*, we have been able to perform comparable experiments which indicate the presence of a similar oxidative mechanism in this organism

First, free parasites utilize the acids of the tricarboxylic acid cycle With the exception of citrate and *cis*-aconitate, these substances are oxidized at about the same rate as is pyruvate itself Parasitized erythrocytes oxidize only those acids without extra polar groups (table VI)

Second, oxidation of pyruvate by free parasites is catalyzed by the acids of the tricarboxylic acid cycle, again with the exception of the tricarboxylic acids themselves (table VII) The dicarboxylic acids catalytically increase both the rate of oxygen consumption and the rate of pyruvate utilization

tion No catalytic effects have been observed with intact parasitized erythrocytes

Third, in both parasitized erythrocytes and free parasites, oxidation of pyruvate is strongly inhibited by malonate. In free parasites, the complete oxidation of pyruvate to CO_2 and H_2O is almost entirely abolished in the presence of malonate. The parasite preparations contain a succinic dehydrogenase which is completely inhibited by malonate. In the presence of malonate, pyruvate and stoichiometric amounts of malate give rise to large amounts of succinate. In free

TABLE VII

Catalysis of pyruvate oxidation in free parasites by malate and α -ketoglutarate

Samples contained 1 cc free parasites, cofactor mixture, and the other additions indicated below, in a total volume of 3.0 cc. Gas phase air temperature 40° , time 60 minutes. Values are expressed in micromoles.

SUBSTANCES ADDED	OXYGEN USED	PYRUVATE USED	ACETATE FORMED	PYRUVATE USED CORRECTED FOR ACETATE
None	7.3			
1 micromole malate	8.5			
Change caused by malate	+1.2			
30 micromoles pyruvate	14.4	18.5	11.0	7.5
30 micromoles pyruvate + 1 micromole malate	19.7	21.6	9.4	12.2
Change caused by malate	+5.3	+3.1	-1.6	+4.7
None	7.3			
1 micromole α -ketoglutarate	9.1			
Change caused by α -ketoglutarate	+1.8			
30 micromoles pyruvate	14.4	18.5	11.0	7.5
30 micromoles pyruvate + 1 micromole α -ketoglutarate	19.3	17.6	8.7	8.9
Change caused by α -ketoglutarate	+4.9	-0.9	-2.3	+1.4

The other pathway for oxidation of pyruvate is conversion to acetate. Intact parasitized erythrocytes form practically no acetate from 0.01 M glucose, the approximate glucose level in chicken blood. It is therefore highly improbable that acetate is a normal product of the metabolism of the malaria parasite *in vivo*. We have accumulated considerable evidence which suggests that acetate is formed from pyruvate only when the organism is flooded with high concentrations of pyruvate or

TABLE VIII

Oxidative formation of succinate by parasite preparations

Samples contained 1.0 cc parasitized erythrocytes of 1.2 cc free parasites and the other additions indicated below, in a volume of 4.0 cc. Substrates were added at a concentration of 0.01 M and malonate at a concentration of 0.02 M. Fumarate was used as a substrate with parasitized erythrocytes instead of malate because it penetrates the erythrocyte more readily. Gas phase air, temperature 40° , time 120 minutes for parasitized erythrocytes and 60 minutes for free parasites. Values are expressed as micromoles per hour per cc parasitized erythrocytes or free parasites. Values for succinate actually represent the sum of succinate and α -ketoglutarate, since the determinations were carried out after heating the samples with acid permanganate to destroy malonate, a procedure which oxidizes α -ketoglutarate to succinate (22).

SUBSTRATES ADDED	MALONATE ADDED	OXYGEN USED	PYRUVATE USED	MALATE USED	SUCCINATE FORMED
Parasitized erythrocytes					
None	-	14.0			0.0
	+	6.5			3.7
Pyruvate	-	42.3	17.7		1.1
	+	14.5	17.7		4.6
Fumarate	-	18.1			0.0
	+	11.3			3.0
Pyruvate + fumarate	-	42.7	14.7		1.0
	+	23.4	18.0		3.9
Free parasites					
None	-	5.1			0.0
	+	1.4			0.2
Pyruvate	-	17.1	19.7		0.0
	+	10.5	19.7		1.5
Malate	-	17.1		17.6	2.2
	+	15.7		16.4	4.9
Pyruvate	-	28.5	18.8	17.6	10.5
	+	26.3	19.0	17.6	11.5

when the mechanism for the complete oxidation of pyruvate is in some manner damaged or impaired. A balance sheet for pyruvate oxidation by the parasite is shown in table IX.

Briefly, then, the carbohydrate metabolism of the parasite involves the anaerobic conversion of glucose to lactic acid by a process of phosphorylating glycolysis and the subsequent oxidation of the lactate in part to carbon dioxide and water by a mechanism similar to the tricarboxylic acid cycle,

parasites, the effects of malonate on pyruvate oxidation are almost completely relieved by stoichiometric amounts of malate or fumarate. Oxidation of glucose and lactate is also strongly inhibited by malonate. These effects are demonstrated in table VIII.

These observations indicate that the malaria parasite *P. gallinaceum* oxidizes pyruvate to carbon dioxide and water by a series of reactions similar to the tricarboxylic acid cycle, which has been demonstrated in pigeon breast muscle, pigeon liver, sheep heart, and in many other organs and tissues. It may be assumed that the enzymes which catalyze these reactions are similar (although not necessarily identical) to those of other organisms, in view of the fact that oxidation of pyruvate in the malaria parasite is accelerated by cofactors known to be involved in the metabolism of pyruvate in other tissues.

and in part to acetate, although the physiological importance of the latter process seems very small

TABLE IV

Balance of pyruvate oxidation

Samples contained parasitized erythrocytes equivalent to 0.8 cc free parasites (carried through the procedure for the preparation of free parasites except for the addition of antiserum) or 1.4 cc free parasites (both preparations from the same sample of blood), 0.01 M pyruvate, 0.00033 M malate, and cofactor solution in a volume of 3.0 cc. Gas phase air, temperature 40°, time 60 minutes. Analytical figures are expressed as micromoles per hour per cc free parasites. Values designated "corrected for acetate" were calculated by subtracting the oxygen and pyruvate used and the carbon dioxide formed in producing acetate on the basis of the analytical figures for acetate and the equation: pyruvate + $\frac{1}{2}$ O₂ → acetate + CO₂. The pyruvate completely oxidized was calculated by dividing the oxygen used corrected for acetate by 2.5, on the basis of the equation: pyruvic acid + $2\frac{1}{2}$ O₂ → 3 CO₂ + 2 H₂O.

	PARASITIZED ERYTHROCYTE	FREE PARASITES
Oxygen used	52.4	23.2
Total carbon dioxide formed	67.1	31.7
Pyruvate used	25.0	18.6
Acetate formed	0.5	6.5
Pyruvate oxidized to acetate	0.5	6.5
Pyruvate oxidized completely	20.8	8.0
Pyruvate accounted for	21.3	14.5
Per cent of pyruvate accounted for	85	78
Respiratory quotient		
Observed	1.28	1.37
Corrected for acetate	1.28	1.26
Oxygen/pyruvate ratio		
Observed	2.10	1.25
Corrected for acetate	2.11	1.65
Activity ratio, free/erythrocytic		
Oxygen consumed		0.44
Pyruvate used		0.74

It should be pointed out that all of the metabolic reactions we have described, and by inference, the enzyme systems which catalyze them, have analogies in other tissues.

We have no assurance, however, that the parasite enzymes responsible for these effects are the same as those responsible for the same reactions occurring in other organisms. Actually, we have some evidence suggesting differences between the enzyme systems involved in parasite metabolism and their analogs in other tissues. We have observed differences in the sensitivity to the antimalarial drugs between parasite enzymes and those performing a similar function in other tissues (20). This may well represent a fundamental difference in the actual composition of the enzyme systems themselves. The further study of this fact may prove to be of the greatest importance in understanding the differential effect of chemotherapeutic agents on the parasite and its host.

We have been concerned here with only one phase of the life cycle of the malaria parasite. With the development of new techniques and increased knowledge of the various stages in the life cycle of the parasite, it may be possible to extend the biochemical work to a study of these other forms. At present the technical problems that must be solved in order to study such seem very formidable.

These data which I have presented to you, while they are admittedly fragmentary, represent the most complete information available concerning the enzymic composition of a member of the Protozoa. It is of particular interest that we have not yet encountered enzymes or metabolic properties of the *Plasmodia* which have not been previously known in other organisms. As yet, none of our data afford any opportunity for explaining the highly specific environmental requirements of the parasite, which shift with each phase of its life history. However, it is perhaps not too optimistic to conclude that we now have the beginnings of a sufficient factual and technical experience to permit us to proceed in such a direction.

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CHEMICAL AND NUTRITIONAL OBSERVATIONS ON MALARIAL PARASITES GROWN *IN VITRO*¹

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Soon after undertaking a study of the biochemistry and metabolism of the malarial parasite and the mode of action of antimalarial drugs, it became apparent that one chief stumbling block that prevented the answering of many questions was the inability to obtain growth and multiplication of the malarial parasite outside of the animal host. Our attention was, therefore, directed towards an attempt to remove this stumbling block. As a result, methods are now available (1) which permit the *in vitro* growth and multiplication of the malarial parasite. The experiments to be described here will deal only with the results obtained from the application of these techniques to *Plasmodium falciparum*.

TABLE 1

Summary of *in vitro* cultivation experiments in which twofold or better multiplication of parasites has occurred in 20-24 hours

CULTURE METHOD	TOTAL EXPERIMENTS	NUMBER OF EXPERIMENTS WITH THE MULTIPLICATION LISTED									AVERAGE MULTIPLICATION
		2x	3x	4x	5x	6x	7x	8x	9-11x		
Rocker dilution	131	28	41	19	14	11	8	6	4	4.1	
Perfusion type 1	51	7	15	12	8	3	5	1		4.1	
Perfusion type 2	53	12	17	12	7	4	1			3.6	
Total	235	47	73	43	29	18	14	7	4	3.9	

With this parasite, we have regularly observed a three- to fourfold increase in population during its life cycle of twenty-four hours. A summary of the experiments performed with the three different culture methods that we employ is given in table 1. A fourfold multiplication is the average for a total of 235 experiments though as high as elevenfold increases have been recorded in a few experiments. It is thus possible to obtain a quantitative as well as a qualitative evaluation and comparison of parasite growth under control and experimental conditions.

One type of study that may be undertaken on parasites grown *in vitro* is an assay of their nutritional requirements. The nutrient medium that we have employed in our culture work is composed

¹ The work described in this paper was done in collaboration with the individuals listed in reference (1), and under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the President and Fellows of Harvard College.

of a mixture of salts, glucose, amino acids, vitamins, purines, pyrimidines, and several other organic components (2). The simplest medium on which growth and multiplication are supported is an isotonic salt solution containing glucose and para amino benzoic acid. In the absence of either glucose or para amino benzoic acid the parasite fails to grow. Maximum growth and multiplication occur however, when the complete nutrient medium is employed. Attempts have been made to fractionate the complete medium into essential and non essential components without success. It is even difficult to show the effect of various blocks of nutrients on growth. In table 2, the results of a typical experiment of this sort are shown. Here the addition of vitamins or vitamins plus purines or

TABLE 2

Effect of nutrients on parasite growth

TUBE	GLUCOSE + PARA AMINO BENZOIC ACID	VITAMINS	PURINES	PYRIMIDINES	AMINO ACIDS	FOLD INCREASE 24 HRS
1	+					3.6
2	+	+				3.5
3	+	+	-			4.2
4	+	+		+		4.2
5	+	+	+	+	+	6.9

pyrimidines to the basic glucose and para amino benzoic acid medium causes but little improvement in the quantitative aspects of growth. When all components are present, the multiplication of parasites is markedly increased. The same results are obtained if the order of addition of the various blocks is changed. For example, the addition of amino acids alone or in combination with one other group shows but little stimulation of growth. Purines and pyrimidines when added together seem to produce the best response of any combination of two blocks of nutrients. Undoubtedly, studies of this sort must be complicated by the fact that the normal serum and red blood cells present in the culture medium contribute unknown nutritional factors. The ideal procedure for such studies would be to employ parasites grown free of serum and the host red cell. This has not been accomplished as yet. One step in this direction has been taken, however, in achieving the growth of the parasite within red blood cells washed free of serum and suspended in a synthetic medium containing 1 per cent crystalline serum albumin. The

presence of albumin seems to be necessary for the maintenance of the integrity of the host red cell during the cultivation period

Another point that it has been possible to establish by *in vitro* cultivation of the malarial parasite is that it will grow and multiply at very low oxygen tensions. Indeed, high oxygen tensions are definitely detrimental to its survival *in vitro*. These facts are evident from the data presented in table 3. When the gas phase in equilibrium with the medium contains 95 per cent oxygen, the parasite fails to multiply and at the end of a 24-hour cul-

TABLE 3
Effect of oxygen tension on parasite growth

O ₂ CONTENT OF GAS PHASE*	NO. OF EXPTS	AV. CHANGE IN PARASITE COUNT AFTER 24 HRS	ABNORMAL AND EXTRACELLULAR FORMS AFTER 24 HRS
%		%	%
0.37	2	+460	5
20.0	4	+310	9
95.0	2	-30	47

* In all cases, 5% CO₂ present, residual gas is nitrogen

TABLE 4
Action of quinine *in vivo*

TIME AFTER INITIAL INJECTION	BLOOD QUININE	TOTAL PARASITES	ABNORMAL FORMS
hrs	mg/L	%	%
0	0	2.4	3
1	22.4	4.5	2
4	22.8	6.8	2
12	11.0	5.5	8
22	5.4	1.6	18
24*		1.1	5
28*	17.2	0.7	43
48	3.8	0.1	60

* At 24 hours, there was injected intramuscularly 300 mg and at 28 hrs 100 mg of quinine dihydrochloride

ture period, nearly half of the parasites present are in poor condition or extracellular. On the other hand, the parasites grow and multiply readily when the gas phase contains as little as 0.39 per cent oxygen. Though growth and multiplication appear to be best at this level of oxygen tension, we have regularly employed in our culture work a gas phase containing 20 per cent oxygen, since this approaches the content of oxygen in alveolar air and thus more nearly duplicates *in vivo* conditions. These results certainly seem to indicate that the malarial parasite does not invade the red cell because it desires an environment with a high oxygen content.

The action of antimalarial drugs upon parasites grown *in vitro* may also be studied. A comparison of the action of such drugs both *in vitro* and *in vivo*

is of interest in connection with the problem of drug degradation that occurs within the animal body in so many cases. Often the question arises as to whether the degradative products or the drug *per se* exhibits the predominant antimalarial action. In the case of quinine and atabrine, it has been found that the same concentration of these drugs is required to suppress the growth of *P. l. novlesi* *in vivo* and *in vitro*. This fact suggests that it is the drug itself which exerts the predominant action. As an example, an experiment with quinine may be presented. When about 2 per cent of the red cells of a monkey were parasitized, blood was removed by venapuncture and two culture vessels were set up adding 10 mg of quinine per liter to one of them. Then the parasitized monkey was given quinine dihydrochloride. One hour later, blood was again withdrawn from the animal and an additional culture vessel set up. Blood

TABLE 5
Action of quinine *in vitro*

TIME	CONTROL—NO QUININE		QUININE ADDED <i>IN VITRO</i> TO GIVE 10 MG/L		QUININE CONTAINING BLOOD DRAWN FROM ANIMAL*	
	Total parasites	Abnormal forms	Total parasites	Abnormal forms	Total parasites	Abnormal forms
hrs	%	%	%	%	%	%
0	1.3	1	1.3	1	1.9	1
5	2.1	5	2.3	8	1.9	7
24	3.4	13	0.7	24	0.4	36

* Quinine concentration by determination 5.6 mg/L

samples were then withdrawn at intervals from the cultures and the animal to determine the levels of quinine and changes in parasite count and morphology. Table 4 shows the *in vivo* action of quinine while table 5 gives the *in vitro* effects. Although the differential effects are not given here, in both the *in vitro* and *in vivo* experiments, there was a definite slowing of the parasite's life cycle. The morphological changes produced by the action of quinine were similar *in vitro* and *in vivo*. Similar data have been obtained for atabrine.

Another example that may be given of the action of a drug upon *in vitro* grown parasites is that of sulfadiazine. In this case, it has been possible to demonstrate the antagonistic action of para-amino benzoic acid against the drug's effect. In figure 1 an experiment is portrayed which illustrates this antagonism. As mentioned earlier, the parasite fails to grow and multiply *in vitro* in the absence of para-amino benzoic acid. This is evident from the data presented in figure 1 for the control culture. The addition to the culture of as little as 10% per cent of para-amino benzoic acid (PAB) is sufficient to produce good growth and multiplication

of the parasites. Larger amounts seem to be less beneficial to growth. However, in the presence of 1000 γ per cent of sulfadiazine, growth does not occur in the presence of 10 γ per cent of P A B. With this amount of sulfadiazine present, growth will result only when the P A B concentration is raised to 100 γ per cent. It should be pointed out

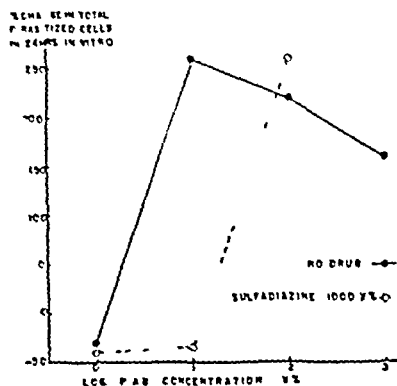


Fig 1 Sulfadiazine para amino benzoic acid antagonism as observed on the second generation of *in vitro* grown parasites

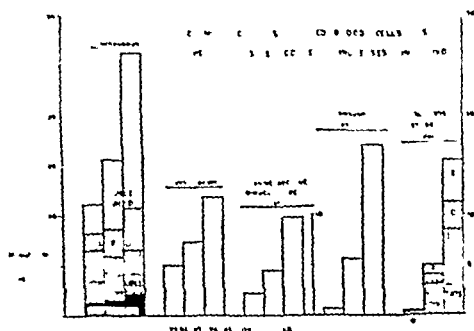


Fig 2 Chemical changes in red blood cells as their parasite content increases *in vitro*

however, that the antagonistic effect of these two substances cannot be observed on the first generation of parasites grown *in vitro*. In the experiment portrayed, the results are for the second generation of parasites, the first generation having been also grown under the experimental conditions given here.

A comparison has also been made of the chemical changes that occur in red blood cells as their

parasite content increases *in vivo* and *in vitro*. The data presented in figure 2 are for *in vivo* changes. This data was obtained by analyzing red cells drawn from a monkey before parasitization and again on two occasions after parasitization when the per cent of parasitized cells had reached 17 per cent and 15 per cent, respectively.

Nucleic acid phosphorus is reckoned as the difference between total phosphorus and the sum of phospholipid and acid soluble phosphorus. With the exception of the acid soluble phosphorus, there is observed a marked increase in all listed components or metabolic process rates for total red cells as the per cent parasitization increases. It may be calculated from the data given that each parasitized cell in this experiment consumes approximately fifty times as much glucose and oxygen as a normal red cell. Somewhat more than half of the glucose that disappears in the presence of parasitized cells is accounted for as lactate and not more than one sixth of the glucose disappearing is completely oxidized. Each parasitized cell in this experiment contains 4 times the fatty acids, 3 times the total P, 2.4 times the 15 minute hydrolyzable P, 3.8 times the phospholipid P, 13.5 times the nucleic acid P, and 9 times the flavin adenine dinucleotide found in a normal red cell.

Comparable studies have been made on *P. knowlesi* grown *in vitro*. The results are similar except for the case of oxygen consumption. Multiplication of parasites *in vitro* has not been attended by the same increase in oxygen consumption that is observed during multiplication *in vivo*. We have, as yet, no explanation for this phenomenon. It should also be pointed out that, though increases in flavin adenine dinucleotide occur during multiplication of parasitized cells both *in vitro* and *in vivo*, an increase of this component has also been observed during culture of normal blood cells *in vitro*. It is thus possible that the increases observed in this component represent synthetic activity on the part of the red blood cell rather than by the parasite itself.

These are a few of the types of chemical and nutritional observations that may be made on malarial parasites grown *in vitro*. Many other questions concerning this parasite remain to be answered. It seems likely that studies made on parasites grown *in vitro* will be helpful in solving some of them.

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METABOLISM OF THE MALARIAL PARASITE

ACTION OF ANTIMALARIAL AGENTS UPON SEPARATED *Plasmodium Lophurae* AND UPON CERTAIN ISOLATED ENZYME SYSTEMS¹LESLIE HELLERMAN, MARIANNA R BOVARNICK AND CURT C PORTER²*Department of Physiological Chemistry, The Johns Hopkins University, School of Medicine, Baltimore*

This review will recount briefly the results of investigations of a biochemical nature that were undertaken in this Laboratory in an effort to gain insight into the characteristics of the action of certain antimalarial agents. The subject matter is based upon the content of several papers dealing with the metabolism and properties of separated, erythrocytic forms of *P. Lophurae* (1, 2) and with the behavior of certain agents (3) with isolated enzyme systems, and in addition a few observations as yet unpublished. The results suggested several explorations of a synthetic nature^{3, 4}. But their greatest interest lay apparently in the observation of interference by quinacrine (atabrine), quinine, and related compounds, under specified conditions, in a transphosphorylation action essential to the utilization of glucose in the *lophurae* organisms, as well as in quantitative data concerning combinations of basic aromatic compounds with a number of specific proteins.

Evidence of a qualitative and semi-quantitative nature forcibly suggests a competitive relationship between quinacrine and adenosine 5-phosphate in *lophurae*. Observations in this Laboratory and elsewhere indicate further that quinacrine, quinine, and various related compounds all share the property of combination with proteins. Certain enzymes are inhibited in processes that may be competitive or non-competitive with respect to the substrates or to prosthetic groups. The effects may be reversible or irreversible, depending upon the nature of the aggressive agent, the affected protein, and the conditions.

The observations appear of some general interest for the action of synthetic and natural therapeutic agents, from the point of view of the malarial problem, they suffer for lack of more com-

prehensive experience of the kind emphasized here in respect to the metabolism of malarial cells of different species and to this extent must be considered preliminary in nature.

Separated parasite material. To investigate more closely the interference of chemical agents with metabolic processes of the parasitic cells, and to supplement studies (4, 5, 6, 7, 8, 9) upon parasitized erythrocytes, it was deemed advisable to attempt the isolation and study of surviving, erythrocyte free malarial parasites of one or more strains, such isolated material to retain in high degree the initial respiratory activity and some stability of activity. This was accomplished (1) with the red cells of duck blood, heavily parasitized with *Plasmodium lophurae*, by the controlled action of saponin, a reagent that previously had been used by Christophers and Fulton (10). There were obtained preparations with an O₂-uptake of 18 to 60 micro liters per 15 min. period for parasites from 0.6 ml. of blood, representing 70 to 90% of the initial respiratory activity of the parasitized red cells. The parasites could be kept at 0° for 24 hours without much loss and they retained some infectivity for ducks. For present purposes they may be regarded virtually as surviving tissue. It will be noted (1) that the success in their separation depended upon the use of a minimal concentration of saponin and a minimal time of action at a temperature, 37°, substantially optimal.

Substrates utilized. The initial respiratory rate was maximal with lactate and pyruvate as well as with glucose. In the case of glucose the rate at the end of the third hour was 80 per cent of the initial, declining slowly thereafter. When in place of one of these substrates, succinate or fumarate was employed, the initial rate was approximately 30 per cent of the glucose rate. Only pure sodium pyruvate was utilized by separated parasites, a marked toxicity with respect to isolated trophozoites (although not apparently to parasitized red cells), observed (1) with improperly prepared solutions, was reminiscent of the experiences of Peters in connection with another problem (11).

In the absence of added nutrient, oxygen uptake was insignificant. When, however, there was added adenylic acid or adenosine triphosphate, an appreciable and rather stable respiratory activity was observed. This effect was attributed tentatively to the utilization under these conditions

¹ The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Johns Hopkins University.

² With technical assistance by Ann Lindsay and Henry Frank Koster, and Harry J. Lowe and J. R. Kimmel, Henry Strong Denison Scholars for 1946-47.

³ Phenazthionium compounds. To be published.

⁴ Derivatives of phenylalanine and of auramine. J. Am. Chem. Soc. In press.

of an intracellular substrate, possibly a polysaccharide

Effect of Reagents The respiratory activity of separated parasites with an initial O_2 uptake of 27 to 35 micro liters per 15 min per 0.6 ml and RQ , 0.83 to 0.93, was abolished by hydrogen cyanide, in consistency with observations of others working with parasitized bloods. The action of the mediator dye cresyl blue, upon normal nucleated erythrocytes was known to be stimulatory, and was observed by us to enhance also the respiratory rate in the case of parasitized red cells, but the dye had a somewhat toxic effect upon separated parasites, reducing the rate approximately 15%. It is interesting to note therefore that superposition of the action of the reversibly reducible dye upon cyanide inhibition resulted in an appreciable restoration of the respiratory activity, both for separated parasites with RQ reduced now to 0.6, and for parasitized red cells.

The effect of quinacrine of initial concentration 0.001 M upon the parasites, whether separated or in red cells, and with glucose or pyruvate, was to reduce the rate of O_2 uptake only 50 to 60 per cent, if the initial concentration was 0.0001 M the per cent inhibition was 20 to 25%. Quinine's effect was still smaller. Negligible moreover was the effect of quinacrine or quinine upon the respiration elicited by cresyl blue after cyanide poisoning.

Somewhat similar results were noted when azide was used in place of cyanide.

These observations suggested that in these parasites the respiratory enzyme (cytochrome oxidase) was normally sensitive to cyanide or azide and little sensitive to the action of quinacrine. They did not appear to be consistent with an hypothesis that the action of certain antimalarial agents was to be attributed in *P. lophurae* to a specific effect upon a dissociating flavo enzyme functioning in the catalytic chain for oxidation.

Detailed results, elaboration of the argument, and bibliographic references are given in (1) and (2). The true concentration of quinacrine in these tests was found by fluorimetric analysis to be of a lower order of magnitude than the initial calculated, owing to combination of the drug with erythrocytic nuclei as well as with parasite substance. The red cell nuclei had been released with the parasites but under none of the conditions used in these studies were found to contribute to metabolic activity.

Sulfhydryl binding reagents, other substances In experiments hitherto unpublished it was found that sodium *p* chloromercuribenzoate, 0.0001 M, stopped oxidation of glucose and of pyruvate in separated parasites, no reversal was realized with glutathione, 0.001 M, although the latter reagent, itself, did not affect the rate. Iodoacetate abol-

ished respiratory activity. Malonate, 0.001 M, caused a decrease of 30% with glucose, and 50% with pyruvate. Glutamate, 0.03 M, phenylalanine, 0.02 M and aspartate 0.003 M inhibited 10, 30, and 10%, respectively.

Oxidation in separated parasites initially depleted of substrate Parasites that had been thoroughly exhausted of substrate were found to oxidize glucose only after an induction period (2). In the presence of quinacrine the oxygen uptake then was strongly inhibited at considerably lower concentrations than had been observed with cells that had not been deprived of glucose. For illustration (2), after restoration of glucose to depleted cells, the rate of O_2 uptake after the first 15 minute period was only 8% that of non depleted organisms. After 30 min, it was 34%. The final (maximal) rate under these conditions was 59%, connoting measurable cellular injury during the period of substrate removal. When quinacrine was added in an initial (apparent) concentration of 0.0001 M either during the period of substrate removal or immediately before glucose, the decrease in the final, maximal rate was 85% (78 to 95% for 21 experiments). With none of the other substrates (see above) was a similar, marked induction period observed. But pyruvate oxidation by depleted cells showed considerable sensitivity to quinacrine.

The induction period was shortened materially in the presence of fumarate, succinate, adenylic acid (adenosine 5 phosphate), or adenosine triphosphate (ATP) the four substances exhibiting comparable effect if added during the period of substrate removal. Action by ATP added simultaneously with glucose was less rapid than by any of the other three substances similarly added, owing probably to impermeability of the cells to ATP, the action of the latter substance under the conditions presumably was predicated upon preliminary hydrolysis to adenylic acid. The final rate with succinate or fumarate was significantly greater than the control, and only slightly greater with adenylic acid, consonant with the observations (1) of an additive action of the first two when used with glucose in contrast to non additive effects in the case of adenylic acid or ATP.

Reversal of the quinacrine "block" by adenylic acid Adenylic acid or ATP was found to exert an almost specific action in preventing the inhibitory effect of quinacrine with respect to glucose utilization in isolated parasite cells initially depleted of substrate. The characteristics of the antagonism suggested a competitive action, the degree of reversibility depending upon the concentration both of quinacrine and adenylic acid ((2), Table III). Some reversal was effected also by fumarate and by succinate. However, protection by the latter two metabolites was observed only when they were

present throughout the test, while adenylic acid acted whether added before or after substrate depletion. The decrease in sensitivity to quinacrine observed in the case of fumarate or succinate was considered to be related to frequent observations that the oxidation of numerous substrates is associated with phosphorylation, tending to maintain a high level of ATP.

As a check on the significance of the measurements of oxygen uptake, glucose disappearance was estimated simultaneously in several experiments. The results from the two methods were in agreement. In contrast to the action of added adenylic acid or ATP in substrate depleted cells was their complete lack of effect upon the quinacrine inhibition of O_2 uptake of cells never deprived of glucose.

Numerous substances were tested and found to have no influence whatsoever upon (a) the rate during the period of depletion, (b) the length of the induction period, and (c) the inhibition by quinacrine. Such substances were yeast adenylic acid (adenosine-3-phosphate), hexose diphosphate (which probably did not penetrate), adenine 0.001 M, spermine or spermidine 0.0004 M, pyridoxine 0.17 mg per ml, flavin mono- and dinucleotides 1.7 γ per ml, cocarboxylase, coenzyme I, and a mixture containing adenine, guanine, uracil, xanthine, thiamine, nicotinamide, nicotinate, p-aminobenzoate, pyridoxine, pantothenate, riboflavin, choline, and ribose.

Action of various agents, adenylic acid as antagonist. The following compounds were found to resemble quinacrine in being markedly inhibitory in a concentration that was only slightly or not at all suppressive with cells never deprived of glucose: quinine, plasmochin, auramine, "novalauramine"⁴ and several others ((2), Table VI). Here also reversal was effected by adenylic acid. Sulfanilamide, 6-methoxyquinoline, and the complex amino acid,⁵ SN 11,527 displayed no suppressive action.

Phosphate distribution. In view of the apparently specific action of adenylic acid in antagonizing the action of quinacrine and certain other compounds in substrate-depleted cells, it was considered of importance to study the alterations in some of the constituent phosphate compounds under various conditions ((2) Tables IX and X). It may be said in general that incubation for 100 minutes in a special egg albumin buffer, without substrate, led to an increase in inorganic and total acid-soluble phosphorus and to decrease in organic and labile phosphorus. On subsequent addition of glucose the

changes in organic, inorganic, and labile phosphorus were reversed partially, unless quinacrine was present in a concentration sufficient to prevent oxygen uptake. Separate analysis of cells and supernatant indicated that no labile phosphorus was ever present outside the cells, although some ester phosphorus did appear in the supernatant. ATP was found to be present in the cellular labile fraction.

Discussion. From the evidence cited above it has been concluded (2) that the induction period in the oxidation of glucose by substrate depleted cells is related to the necessity for phosphorylation of glucose before this substrate can be utilized, and that quinacrine and certain other agents interfere with this phosphorylation, possibly by competition with adenylic acid, ATP, or both. This hypothesis is consistent with observations suggesting that the carbohydrate metabolism of *Plasmodium lophurae* resembles markedly that of other cells, e.g., mammalian tissue cells. The latter assumption would receive general support also from studies such as those of Speck and Evans (12) who extracted from preparations of *Plasmodium gallinaceum* various enzymes that displayed properties similar to those involved in the metabolism of tissue cells. It is of interest that isolated hexokinase of *gallinaceum*, catalyzing the phosphorylation of glucose by ATP, was found to be notably sensitive to the action of quinacrine. The antagonism to the effect of quinacrine by adenylic acid or ATP observed in the present investigation suggests that quinacrine may compete with one or both for an enzyme protein. This concept, rather than the possible combination of the drug with a coenzyme of phosphorylation, appears to fit best the available experimental facts, although the matter will be scrutinized further. In cells already metabolizing glucose the relatively lower degree of inhibition by quinacrine is found to be unaffected by an increased adenylic acid concentration. The latter substance probably is maintained chiefly as ATP during a process involving continuous oxidation. Thus, in parasitized red blood cells incubated for several hours without added substrate the absence of an induction period and of significant inhibition by quinacrine of the oxidation of glucose may also be attributed to conservation of ATP accompanying their slow but continuous utilization of glucose. This may underly also the beneficent action of fumarate in separated parasites depleted of glucose.

With respect to *in vivo* action, it is conceivable that certain antimalarial drugs might cause interference with some phosphorylation reaction essential to the life or reproduction of the cell. Such a process would not necessarily be rate-limiting with respect to respiration. It is important to recall in this connection that there has been

⁵ The Survey number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs, antimalarial activities are tabulated in a forthcoming monograph edited by F. Y. Wiselogle.

observed in the action of a rather wide variety of enzymes some degree of sensitivity to quinacrine and other antimalarial drugs. The general reactivity of certain agents with respect to specific proteins will be discussed presently.

Concerning the mode of action specifically of antimalarial drugs, we have presented from this phase of the exploration only certain effects in parasitic cells under a limited set of conditions, and obviously have not dealt with certain other matters of great practical and theoretical importance. These aspects, many of which have been treated adequately by other investigators, include biochemical considerations regarding absorption, physiological distribution, plasma and tissue levels, degradation and destruction of agents, elimination, etc. We have omitted discussion of possible synergistic effects in the metabolism of parasites and the host red cells. Certain physical chemical properties of the drugs in relation to physiological action are under investigation.⁶ A number of perplexing and interesting matters that arise from the study of interference with the action of quinacrine under a variety of conditions in living organisms have been reviewed recently (13).

Action upon several isolated enzymes. The objectives of this phase of the investigation have been presented (3). Observations of the potential interference of various agents in the metabolic processes of "surviving", isolated cells have been paralleled by studies of reversible and irreversible actions of such compounds upon several isolated enzymes. In a few cases the investigation has proceeded far enough to merit consideration here. Certain correlations in the behavior of quinacrine, quinolines, and a number of related compounds can be made the basis of further studies of biochemical action.

The evidence cited earlier suggested no unusual sensitivity to the action of quinacrine of the respiratory enzyme and the cytochromes of *P. lophurae*. Further general information concerning the iron-containing enzymes was provided in a study with crystallized catalase of beef liver. With the use of a manometric method, at 30° and pH 6.6 (potassium phosphate), concentrations of catalase and hydrogen peroxide were so adjusted that the decrease in the substrate was first order during the first ten minutes. Conditions then were arranged so that hydroxylamine in a concentration of 1.55×10^{-6} M was required to double the half period. With this designated as 100, the relative inhibition by toluidine blue, methylene blue, orthochlorophenol, indophenol and thionine, all metal free, was observed to be only 1.35, 0.7, 0.02, and 0.009, respectively. Quite negligible under the same con-

ditions was any effect by quinacrine, quinine, or quinine methochloride. Under another set of conditions where methylene blue inhibited 78 and 53 per cent when 0.001 and 0.0001 M, respectively, the inhibitory effect with 0.001 M quinacrine was 5 per cent and with 0.001 M quinine, zero.

Lipase. The sensitivity of lipases to quinine has been known for some years. Rona found that the rate of tributyrin hydrolysis was decreased significantly by quinine in low concentration when serum or pancreatic lipase, but not liver or kidney lipase, was the catalyst. Other workers have observed variation in the sensitivity of lipases derived from various organs of different species. An extensive investigation is that of Iulston (11). Using the drop method, with tributyrin as substrate, he tested the effect of some of the cinchona alkaloids and also synthetic antimalarials and observed marked depression in lipase activity particularly in the case of the enzymes of monkey and human sera.

We have used a purified pancreatic lipase and a manometric method of satisfactory precision. We need not encumber this review with complete detail, but it should be stated that reaction mixtures contained bicarbonate-carbonic acid buffer, sodium and potassium chlorides and sodium cholate, in an atmosphere consisting of carbon dioxide, 5 per cent, and nitrogen, 95 per cent. Action upon triacetin was not slowed by quinine or quinacrine, but the rate of hydrolysis of tributyrin was depressed markedly in the presence of quinine, quinidine, cinchonine, cinchonidine, quinacrine, and the 4-aminoquinoline derivative, SN 6911, moderately by quinine methochloride, 6-methoxyquinoline, and diethylaniline, and not significantly by di-*n*-butylaminopropanol and the sulfonamides. Quinacrine or quinine, 0.001 M, drastically slowed the hydrolysis of triacetin and tricaprylin.

Lipase, under the conditions used in this work, was unaffected by iodoacetamide, glutathione, cysteine, cyanide, urethane, Ca^{++} , Mg^{++} , or Mn^{++} ions, it was inactivated more or less by Zn^{++} and Cu^{++} ions and by mercuric chloride and sodium fluoride, also by action during 30 minutes of *o*-iodosobenzoate and *p*-chloromercuribenzoate. These results gave little indication as to the nature of an active and especially sensitive group.

Of the antimalarial drugs studied, among which were included those identified by Survey Numbers⁷ 5900, 5949, 1796, 6520, 7275, 4085, 4517, and 7191, all in 0.003 M, only those containing the quinoline or acridine nucleus proved to be lipase inhibitors. However, methylene blue was slightly depressant, while 7-di-*n*-butylamino-3-diethyl-

⁷ SN 5949 is a 1,4-naphoquinone derivative, SN 1796, a tetrahydrophenanthrene-methanol compound.

⁶ Irvin, J. L., private communication, cf. Irvin, J. L. and Irvin, E. M., Fed. Proc. 5: 139, 1946.

amino-1-methylphenazthionium chloride,³ SN 8285, a dye reported⁵ to possess an activity 4 Q with respect to *lophurae* or *calhemerium* infections in ducks, was powerfully inhibitory. But, marked depressant action was manifested also by the members of a group of non-antimalarial acridine compounds (SN 4472, 2667, 4402, and others) possessing a nucleus identical with that of quinacrine but differing structurally from quinacrine in respect to the substituent in position 9.

It has seemed most reasonable to suppose that the action of the several lipase inhibitors was directly upon the enzyme-protein. With quinacrine, quinine, and the dye, 3-diethylamino-7-mono-*n*-butylamino-1-methylphenazthionium chloride³, it was found that the effects could be formulated as reversible inhibitions. Here the data fitted well the expression,

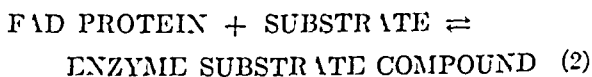
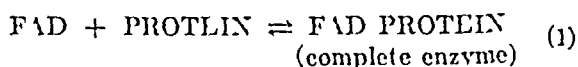
$$\log K = \log \frac{100 - \% \text{ inhibition}}{\% \text{ inhibition}} + \log [\text{inhibitor}]$$

For quinacrine, the value of $\log K$ varied -3.28 , -3.55 , -3.79 , -3.67 , -3.55 , -3.58 , average, -3.6 , in the concentration range 1×10^{-4} to 3×10^{-3} M, while $\log K$ for quinine was -3.31 , -3.30 , -3.19 , average, -3.3 . For quinacrine⁸ and quinine respectively, the concentrations $\times 10^4$ for 50% inhibition were 2.5 and 5.

Lactic dehydrogenase, heart flavoprotein (15)
There resulted a small inhibition of the dehydrogenase by compounds SN 6911 and SN 7618 only when the concentration of Coenzyme I in the reaction mixture was extremely low (1.6×10^{-5} M), and a lesser effect upon this protein by quinacrine and quinine. Effects upon the linking flavoprotein were observed in the presence of excess dehydrogenase and a low concentration of flavoprotein, the action of which under the conditions was the limiting factor. Here the flavoenzyme was inhibited appreciably by quinacrine and SN 6911 and less significantly by quinine and SN 7618. Only slight inhibitions were observed with compounds⁷ SN 5949 and 1796, and with sulfanilamide. The inhibitions appeared to result from reversible combinations with the enzyme, inasmuch as the data conformed well with the theoretical relationship presented above ($\log K_{\text{QUINACRINE}} = -2.5$). It was observed also that the quinacrine inhibition was non-competitive as regards the "substrate" for heart flavoenzyme, namely Coenzyme I. Moreover the inhibition could not be prevented by the addition of flavin-adenine-dinucleotide (FAD). This points to a distinction of considerable importance in

the effects with heart flavoenzyme, on the one hand, and cytochrome reductase of yeast (16) and d-amino acid oxidase on the other. The latter are dissociating flavoenzymes, the specific protein constituents of which were "protected" from the action of quinacrine and related agents in the presence of an excess of the appropriate flavin nucleotide. The heart enzyme, under diverse conditions explored in this work, was non-dissociable, certainly in the pH range 5 to 7, only in processes involving denaturation of the complete enzyme was the prosthetic group removable.

Amino acid oxidase. The d-amino acid oxidase was given particular consideration (3) in these studies because it is a readily available and reasonably stable representative of the flavoenzymes capable of dissociation. Furthermore, the observations of Wright and Sabine (17) and of Haas (16) conveyed suggestions that quinacrine *in vivo* might be capable of a rather specific competition with flavin nucleotides for one or more essential enzyme proteins. The reversible processes concerned in the functioning of d-amino acid oxidase, of especial interest here, are



With kinetic methods a number of investigators (18, 19, 3) have found that the dissociation constant K_T at 37° for Process 1, is of the order 5×10^{-7} mole per liter, and K_S for Process 2, 0.005 mole per liter. It is known that the enzyme's activity may be modified by the action of certain well-defined anionic inhibitors through reversible competition with the substrate (Process 2), and it is observed now (3) that inhibition is effected also through competition with FAD for the specific protein (Process 1) of quinacrine, quinine, and a whole series of aromatic nitrogen compounds. The action of quinine has appeared to be quite reversible, the dissociation constant, K_Q , being of the order 5×10^{-4} mole per liter. With quinacrine there appeared to be also an irreversible stage. The relative combining effects of various agents, as compared with that of quinine, placed at unity, were evaluated semiquantitatively ((3), Table II) as auramine 7, quinacrine 2.5, novolauramine 2, a series of antimalarial and non-antimalarial quinoline compounds 0.5 to 1, sulfonamides 0.04 to 0.2, and pyridine, aniline, etc., 0.04 or less. The reversible effects discussed above were independent of the "sulfhydryl character" of the separated protein. They were essentially unrelated also to the drastic denaturant action of certain phenazthionium compounds (3).³ The study of auramines⁴ was sug-

⁸ Dr. Chandler McC. Brooks has informed us that he has investigated a possible effect of quinacrine under certain conditions upon fat metabolism in rats, and has found no evidence of interference by this drug.

gested by this work. Novolauramine displayed some antimalarial activity while a number of related compounds including auramine, itself, did not.

Conclusion. It was not anticipated that studies with isolated enzymes, whether from parasitic cells or otherwise, would provide immediate definitive clues concerning the mode of action of therapeutic agents. It was considered, however, that intensive investigation should afford suggestions concerning the control of enzymatic activity, particularly in relation to interference by various classes of reagents with the metabolic processes of cells. Results from flavoenzyme studies did not uphold an hypothesis of a specific antagonism between quinacrine and IAD comparable to the so called sulfonamide *p*-aminobenzoate relationship. They did indicate, together with the few results in hand from experience with other enzymes, that quinacrine, quinine, the sulfonamides⁹ and certain other aromatic nitrogen compounds all belong to a class capable of combination, reversibly or irreversibly, with proteins. The combination might, with certain enzymes, result in competition for a prosthetic group, such competition

would not necessarily be related to a close structural similarity between inhibitor and prosthetic group. Combination with an enzyme might not result in inhibition if the portion of the molecule affected is unessential for activity.

It was found in general that the aromatic basic inhibitors behaved similarly with the different enzymes, an enzyme affected by one was affected by all, the order of effectiveness being similar to that with amino acid oxidase. This might be taken as evidence that there are involved here similar combining groups in the various proteins. It is of additional interest that the relative ability of quinacrine, the quinoline compounds, and the sulfonamides to combine with serum proteins is analogous to the order given. Quite aside, moreover, from the intrinsic interest in these observations for enzyme chemistry, the use of the enzyme as an instrument for the evaluation of certain general properties of proteins would appear to present interesting possibilities. It is anticipated that some of the conclusions from kinetic studies will be susceptible of test by direct equilibrium methods.

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* Cf. (20)

THE INFLUENCE OF NAPTHOQUINONES UPON THE RESPIRATORY AND CARBOHYDRATE METABOLISM OF MALARIAL PARASITES¹

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A large number of compounds containing the 3-hydroxy-1,4-naphthoquinone nucleus have been found by Richardson and Hewitt (1) to possess marked antimalarial activity against *P. lophurae* infections in ducks. Several of the more active compounds, as judged by tests on ducks, also suppress *P. knowlesi* infections in monkeys (2). However, the compounds of this chemical type which have been tested for antimalarial activity in humans were found to be either totally inactive or only slightly active (3). Thus it became of importance to determine whether the several animal hosts handle these compounds differently or whether there is a true species specificity with regard to the antiplasmodial activity of the naphthoquinones. Indeed, Brodie (4) observed that degradation products of SN-5090 and SN-5949 accumulate in the blood of patients to whom these compounds are administered. Fieser and coworkers (5) have isolated and characterized many of the metabolic degradation products of the naphthoquinones.

As one possible approach to an understanding of the mechanism of action of the naphthoquinones, we have studied their *in vitro* effects upon *P. knowlesi* and *P. lophurae*.

In summary, it was found that many of the naphthoquinones depress the oxygen uptake of these *Plasmodia*. Of 76 compounds tested *in vitro*, 69 have shown relative antirespiratory activities which roughly parallel their relative antimalaria activities, as judged by suppression of *P. lophurae* infections in ducks. Good agreement between *in vitro* and *in vivo* relative activities is usually obtained when the substituent group in position 2 is a normal alkyl radical, an isoalkyl radical, a tertiary alkyl radical, a methyl, dimethyl or ethyl substituted alkyl radical, an unsaturated alkyl

radical or a cycloalkyl radical. Six compounds which have considerable antimalarial activity in ducks fail to inhibit oxygen uptake of *P. lophurae* or inhibit it only at very high concentrations. The substituent groups in three of these six compounds contain a phenyl radical. The other three compounds are pyridine substitution products. The serum from ducks which have received compounds active both *in vitro* and *in vivo* is strongly inhibitory of *P. lophurae* respiration. Serum from ducks which received two of the above mentioned inactive compounds had no effect upon *P. lophurae* respiration.

Employing duck erythrocytes parasitized with *P. lophurae* as test material, we have made the following observations regarding factors which influence the action of naphthoquinones:

1 Inhibition of respiration becomes evident immediately after addition of an appropriate concentration of an active compound.

2 The inhibition of respiration is readily reversible in the early stages.

3 The oxygen uptake of the parasite-naphthoquinone system is unusually sensitive to variations in pH. Over a range of pH which includes physiological values, unit decrease in pH produces approximately a ten-fold increase in antirespiratory activity of the eight compounds which have been tested.

4 The concentration of a given naphthoquinone required to produce 50 per cent inhibition of oxygen uptake of the parasites depends upon the composition of the suspending medium. The concentration of SN-5090 required to inhibit (by 50%) the oxygen uptake of parasitized cells suspended in human serum (2.7×10^{-5} Molar) is 20 to 30 times as large as that which is required to have an equal effect upon cells suspended in duck serum. One compound has been found to be equally active in duck and human sera. Certain other compounds are more than 100 times as active in duck serum as they are in human serum. Differences in activities of the naphthoquinones are much smaller in Ringier's solution than in serum.

Inhibition of oxygen uptake of *Plasmodia* results principally from interference with carbohydrate oxidation. Whereas normally a suspension of cells containing *P. lophurae* does not show aerobic glycolysis, lactic acid accumulates in suspensions containing an active naphthoquinone in proportion to the degree of respiratory inhibition. Oxidation

¹ The work summarized in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Tennessee.

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of lactate to pyruvate is inhibited by effective naphthoquinones

The respiratory and carbohydrate metabolisms of normal duck erythrocytes are influenced by naphthoquinones in essentially the same manner as those of parasitized cells. However, more than 100 times as high a concentration of SN-5919 is required to inhibit the respiration of normal cells as 50 per cent is required to affect equally the oxygen uptake of cells containing *P. lophurae*.

These observations have led to the development of a biological method by which the rate and extent of metabolic degradation of the naphthoquinones can be determined. The procedure has been to extract the naphthoquinones from the plasma of a patient receiving the drug and to compare the antirespiratory activity of the extracted material with that of the undegraded drug.

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PHYSIOLOGY IN NORTH AMERICA, 1945

SURVEY BY A COMMITTEE OF THE AMERICAN PHYSIOLOGICAL SOCIETY

E. F. ADOLPH, *Chairman*, T. E. BOYD, J. H. COMROE, JR. AND PHILIP DOW

INTRODUCTION

PHILIP BARD

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At a meeting of the Council of the American Physiological Society held in May, 1945 it was proposed that some attempt be made to assess the state of physiology in North America. There were good reasons for this suggestion. At no time since the founding of the Society in 1887 had there been any formal appraisal of the status or the trends of physiology in the part of the world from which our ordinary members are drawn. Yet during the last thirty years, despite the splitting off of physiological chemistry and pharmacology as independent sciences, physiology has greatly extended the front of its attack on biological problems. It has learned to appreciate and to use the intellectual and technical tools of modern physics, chemistry and mathematics. During this same period the physiological point of view has become dominant in the thinking and the doing of leaders in clinical medicine, pediatrics and surgery, a development which has certainly augmented the responsibilities of physiologists. The last three decades have also witnessed an inevitable but bewildering and doubtless deleterious fragmentation of physiology into subdivisions. The War further complicated the status of physiology. It diverted, disturbed and even distorted the activities of most physiologists. In the United States it virtually put an end to the recruitment and proper training of young physiologists. The War also augmented and ac-

celerated the experimental yield in several important sectors of physiology and it hastened the development of new and useful technical procedures. The contributions of scientists to the War effort have caused both government and industry to eye science with a new and provocative interest, physiologists may well ponder the significance of this for the future of their profession. In view of these and other facts and impressions it seemed clear that the taking of an inventory promised to lead to disclosures which would be of general interest to physiologists and might enable them to discharge their growing responsibilities with greater insight and effectiveness.

These were some of the considerations which led the Council in May, 1945 to appoint a fact finding committee to survey the status of physiology in North America and to submit to the Society a report with recommendations. The Committee was composed of Drs. E. F. Adolph, Chairman, T. E. Boyd, J. H. Comroe and Philip Dow. Arrangements were made to have their report presented to the Society at the Atlantic City Meeting of the Federation. This was done. The crowding of the large hall in which this symposium took place showed the wide interest the subject commanded. Each member of the committee spoke on one aspect of the subject and the four presentations were excellently integrated. The liveliness of the

discussion and its prolongation far into the night testified to the audience's appreciation of the report. The thanks of the Council and of the Society for the extent and quality of the efforts of the Committee are here acknowledged.

On recommendation of the Council of the Ameri-

can Physiological Society, *Federation Proceedings* now presents for wider consideration the four parts of the report given at Atlantic City on March 13, 1946. In addition it publishes a paper by Doctor Adolph on the future of physiology which the Committee had planned to include in its report.

SECTION I PURPOSES AND METHODS OF THE STUDY

E. F. ADOLPH

The University of Rochester

The science of physiology has undergone a remarkable development in North America. What are the social mainsprings of that development? How does physiology compare with other sciences yesterday and today? What departures can be anticipated in the near or distant future? Is there more remarkable development to be promoted by wise collective action? These and many related questions have concerned the survey committee in its study of the status of physiology. We believe every adherent of physiology will find important information, and possible stimulation to thought, in the materials to be presented.

The science of physiology has its concrete embodiment chiefly in those who profess it. Its deeds perhaps could be counted in publications, but its present and future lie in the *individuals* who work in it. About them facts can be collected, their numbers and activities can be counted. From trends and present circumstances, certain projections or extrapolations can be carried into the future.

Physiology like all sciences is the property of all people. It was not made in America, but Americans are actively contributing to it. Nothing would have pleased the committee more than to include in this survey information about all persons on the face of the earth who contribute to physiology. That task only an international organization could attempt to perform. It seemed preferable to do what we quickly could for one continent (North America) which contains only 8 percent of the earth's human inhabitants. The same war that has impeded communications to the extent that many physiologists of other continents have not been heard from for 5 or 6 years, has also brought scientists to a present impelling need to take stock of themselves and their ambitions.

Physiologists would gladly merge themselves into the product of their labors, so that the talk could be about physiology instead of about physiologists. We can do little to deal impersonally with that body of abstractions constituting physiology, for abstractions are hard to count, weigh,

and measure. Estimates of them and their significances could be made, but we who would make them are by definition biased about them. For, a physiologist is none if he does not think his science will enlighten the world.

It is the privilege and the responsibility of physiologists to plan for the future. If the members of the profession do not agree concerning what is needed for successful work, what understanding of life can be furnished to mankind, and what services can be rendered to a society that supports us, we would be leaving to the layman, and particularly to the harassed politician, the assessment of values in this science. Success in our work depends today not only upon our prowess in laboratory and library, but also upon our awareness of our place in the social structure. To be intelligently aware requires all the facts we can gather about ourselves in relation to the earth's population which underwrites our work. The facts that could be gathered now—both from published sources and from the returns of a questionnaire, are the grist for the present study.

To understand our science in the midst of our culture, we need to know how physiology began and grew, what of its achievements are most worthy of emulation, which are its leading concepts, and where and when its fruitings are most favored. To assess ourselves, we want to understand where physiologists come from, what they do for a living, where they live and work, what institutions support them, what physical equipment they lack, which ambitions urge them, and how they regard the future. It is obviously impossible to derive complete answers to all these points—even were all the facts in, understandings would still be partial. But such is the scope of this inquiry, and here are the provisional answers. May the inquiry continue to develop in the mind of every physiologist.

What is physiology? Everyone has his individual definition of physiology, and his definition of today is not the same as yesterday's. What would

Haller or Beaumont think if one of us told him how we define physiology?

At the present time physiology is generally considered to be one of the life sciences, a subdivision of biology. It is usually said to be the study of processes in living units. For historical reasons it is often limited to animal units when not qualified by the adjectives plant, bacterial, etc. The concept of animal units varies greatly, and a large advance might be made if representatives of every living species could be induced to become physiologists. Physiology is intimately concerned in many applied sciences, such as medicine, pharmacy, and agriculture, in addition to being a well-developed branch of culture and intellectual endeavor.

For the practical purposes of this report, physiology will correspond to the various labels used for it among institutionally minded people. Hence it has several definitions, and those who belong to it by profession will inevitably characterize it. Some institutions have departments of physiology, hence what goes on in them defines it. There are universities, industries, buildings, societies, foundations, titles of appointments, and publications that use the word each confers a meaning that must be given some recognition in a survey.

Since the survey is mostly concerned with the individuals who profess the science, all who profess it can be accepted in part as representing it. But the same person at one time both is and is not a physiologist. Thus, our American Physiological Society is, quite properly, blessed with many members who, while belonging as enrollees, disclaim any other affiliation with physiology. They may be major contributors to the understanding of animal processes yet have been trained in another discipline, belong to some other department, have an appointment of another name, and publish work in journals of other titles. All this is a mere matter of nomenclature, yet no one can untangle it except in a highly arbitrary manner, and the practical solution is to recognize a particular population of physiologists according to each of the above criteria, including the criterion of the individual's explicit choice. These many populations overlap enormously, yet few individuals answer to *all* definitions of physiologist. We do not speak therefore of insiders and outsiders, but of physiologists according to criterion A, physiologists according to criterion B, etc.

By the same token, the survey is not intended to segregate physiologists from others. It considers groups of scientists who center around this flag of physiology. It studies a sample of biological scientists and infers that devotees of other disciplines are similar in most respects. Instead of setting physiologists apart, instead of encouraging the notion that they are the elect, the sur-

vey may even serve to disperse them among the professional population at large. These several statements may help to clarify the following presentation of what physiologists are today and what they may be tomorrow.

Historical development in America. Physiology like all other subjects of study arose in the dim unrecorded past. Observations and concepts that we would today include in physiology were recorded by Alcmaeon and Hippocrates about 2400 years ago. Major researches were executed by Galen 1750 years ago. The name physiology was attached to the study of organismal processes by Jean Fernel (1542). This subject matter was recognized as a field of instruction about 1700 by Boerhaave in Leiden, who taught it under the title of Institutes of Medicine, meaning the foundations of medicine. The transition to use of the term physiology came gradually during the century and a half following.

Physiology as now recognized came to America as part of medical instruction, the first professor of physiology having been appointed in 1768. It was almost nothing else but a didactic subject until 1850. Isolated individuals in America reported observations and concepts before that date, outstanding ones being John Linnaeus of South Carolina (1743) who studied the daily exchange of matter in relation to weather, Benjamin Franklin of Pennsylvania (1758) who enunciated clearly the principle of body cooling by evaporation of sweat, John Leigh of Virginia (1786) who experimentally inquired into the properties of opium, and William Beaumont (1833). Beginning with the work of J. W. Draper (1844) on the organization of plants, major contributions to physiology appeared almost annually, those who pursued experimental researches being chiefly medical men with other concerns and no laboratory facilities. Their deeds have been told by Billings (1876), Meek (1928), Fulton (1946) and others. Physiology was first taught by a full-time physiologist (J. C. Dalton) in 1854, and by means of laboratory instruction for all medical students about 1887. Attempts to teach physiology in elementary schools, in agriculture and in physical education developed meanwhile.

Investigation in physiology received much impetus from morphology and chemistry, which were developing laboratories, and demonstrating the values of scientific research, within American academic precincts.

The founding of the American Physiological Society in 1887 may be taken to mark the maturation of physiology in North America. It was founded with the express object of furthering the investigation of vital phenomena. The previous century, in which physiology was limited to being a subject of instruction, had failed to develop a need for intimate association among its professors.

Nevertheless, in the hands of the very teachers of the subject, investigation was destined to develop

When the American Physiological Society was founded the population of North America was less than half of what it is today. Geographical pioneering was nearly ended, and wealth had accumulated to a point where institutions of learning could be supported from both private and public funds. Demands for better medical schools were made acute by the organization of state boards of medical examiners in the previous decade.

The history of the Society represents, therefore, most of the history of investigation in physiology in North America. It was reviewed at the time of the fiftieth anniversary (Howell, 1938). We here present a few aspects which can be numerically

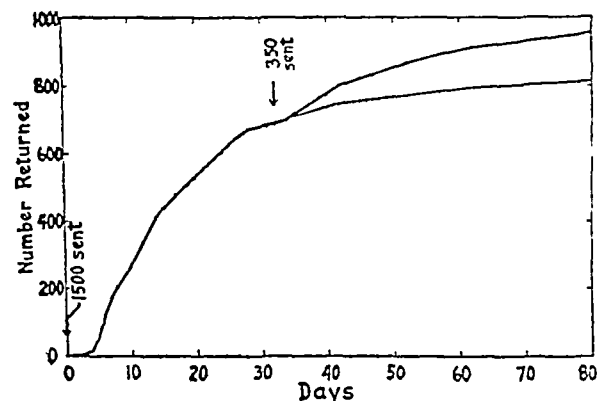


Fig 1 Course of returns of American Physiological Society questionnaire

analyzed, and which lead to a better understanding of the present position and future prospects of American physiologists.

The questionnaire. The survey committee made short work of the need for defining physiology, by using the label of physiology much as it is understood in university circles. Dr. Dow undertook to make a card roster of North American physiologists to whom questionnaires might be sent. The list included over 3000 names, from which 1950 names were selected as a mailing list. A great many of the persons addressed did not admit to being physiologists.

In the end much of our information was correlated with the following categories: (1) Persons who chose physiology as their one preferred field of attachment, (2) Persons who were members of departments labelled physiology. For most items the information gathered was actually no different for outsiders than for insiders of one of these designations.

Returns from questionnaires are never very perfect. Many persons believe all questionnaires are pests. The same persons often fail to distinguish among facts collected by mail, opinions

voted without poll-tax, and advertising in rhetorical questions. Some non-answercers are not enthusiastic about the future.

The American Chemical Society took a poll of professional status of 33,000 members in 1914 (Fraser, 1911), it got 70% returns in 48 days. Its addresses were up-to-date and its members had previous experience with the Society's questionnaires.

We sent out 1500 blanks on December 14, 1915. Later about 150 additional blanks were mailed. The questionnaire itself is shown herewith. Returns arrived in Rochester, N. Y. according to the pattern shown in figure 1. Eventually 1013 replies

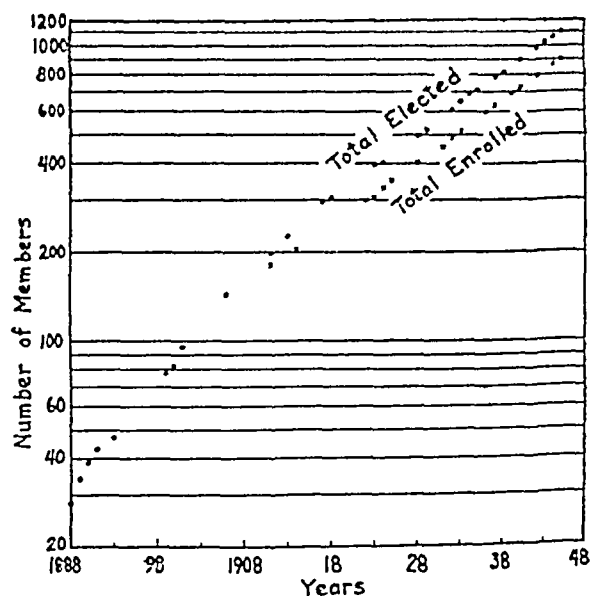


Fig 2 Membership of American Physiological Society

(54%) turned up. In 38 days we had 50% returns from the first 1500; this sample is believed to be representative in most respects. These returns were analyzed chiefly by the punch-card system and sorting machines located in the University of Rochester's Bureau of Educational Statistics, to which Bureau the Committee is deeply indebted.

Each return was entered on two cards, Part I of 48 columns and Part II of 62 columns, with 10 possible places or categories in each column. For each item of information (or column) cards can either be sorted into categories, or the number in each category (row) be registered on a counter, or all rows can be tabulated in order.

Present trends. One measure of the developments among physiologists is the membership of the American Physiological Society. The number of members has increased along the course shown in figure 2. From the original 28 members the number has multiplied to 905 living members in 1945. In those 57 years a total of 1115 persons have been

FEDERATION PROCEEDINGS

December 1 1945

To Physiological Scientists of North America
 The Council of the American Physiological Society desires a survey of physiology at the post-war crossroads. The Committee named below is undertaking to assess the position of physiology in an effort to foretell future developments.

The first task of the Committee is to collect information about physiologists in diverse occupations. It is desired to include many persons who do not happen to belong to the American Physiological Society. Equally, it is impossible to include all who teach upon physiology. A coded system is employed to make answering brief and easy.

The Council and the Committee ask you to fill the accompanying questionnaire. A coded system is employed to make answering brief and easy.

The information to be derived from the answers to this questionnaire comprises:

1. Composition and distribution of the North American population of physiologists;
2. Where physiologists come from and what becomes of them;
3. What practical needs are felt in teaching;
4. What practical needs are outstanding in research;
5. How physiology is supported financially and institutionally;
6. What livelihoods are available to physiologists;
7. Available sources of information have already been utilized; the National Register of Scientific Personnel, American Men of Science, and others. They do not suffice for the purposes mentioned. Hence this questionnaire has been framed.

Information about incomes is asked for, not because the Committee wishes to pry into anyone's personal affairs, but because we think it important, at the present time of economic readjustments, to find out what physiologists are being paid. The figures on individual incomes will be kept confidential and actually will be seen only by a computer who is not a member of the Committee. The questionnaires as they are returned will first be given to her; she will detach Part I from Part II.

We hope to complete the work in time to make a report at the next meeting of the Federation. Please help us by returning your questionnaire promptly in the addressed envelope.

Council:
 Philip Bard, President
 Wallace O. Fenn, Secretary
 Mallorrell Davis, Treasurer
 Laurice B. Vissler
 Charles H. Best
 Miriam E. Essex
 William F. Hamilton

Committee:
 Edward F. Adolph, Chairman
 T. E. Boyd
 Julius H. Comroe, Jr.
 Philip Dow

AMERICAN PHYSIOLOGICAL SOCIETY Questionnaire

This questionnaire is in two parts. All of Part I is coded for statistical treatment, and your name need not appear on it. It will be detached from Part II as soon as we receive it or if you prefer you may mail it separately in either case anonymously, is insured.

Part I

Please read each question carefully and completely before answering any part of it. Then circle not more than one code number under each question or division of a question. Disregard figures in column at left of code.

- 1 Educational levels. Circle below the one code number that corresponds to the highest educational level reached by you:
 Ph D or Sc D first then M D or Sc D
 M D first then Ph D or Sc D
 Ph D or Sc D (physiology)
 Ph D or Sc D (other science)
- 2 Have you had any special training in physiology or in a related field other than that implied in your degrees or acquired in the ordinary course of your employment?
 a Amount
 None
 One year or less
 One to two years
 Two to four years
 More than four years
 b Subject
 Physiology
 Other field
 Both
- 3 Place
 1 In North America
 2 In foreign countries
 3 Both

3. Year of entering profession

- (1) If you hold the Ph D or Sc D degree, circle below the year in which it was awarded, or
 (2) If you do not hold the Ph D. or Sc D degree, circle the year in which you consider yourself to have entered your professional career:

5-6 1899 or before
 19 --00 01 02 03 04 05 06 07 08 09 10 11 12 13 14 15 16 17 18 19
 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39
 40 41 42 43 44 45

4 Shifts between physiology and related fields During your professional life have you

- 7 Worked continuously as a professional physiologist? 1
 Entered physiology from a related field, and
 Remained thereafter in physiology? 2
 Transferred again to another field? 3
 Left employment as a physiologist to enter a related field and
 Remained in fields other than physiology? 4
 Returned to physiology? 5
 Never worked as a professional physiologist? 6

5 Wartime status and postwar employment prospects

a During World War II, did you

- 8 Remain at your prewar position? 1
 Enter government service, part time, as a civilian? 2
 Both? 3
 Become a member of the armed forces? 4
 Enter government service, full time, as a civilian? 5
 Change to a new position not in government service? 6

b If you changed employment at all during the war, whether you entered government service or not, do you consider your present employment to be

- 9 Permanent? 1 Temporary? 2 Or are you now unemployed? 3

c If you entered any kind of temporary employment during the war (including service in the armed forces, if you expect to be released), indicate the item below that best describes your present prospects of employment

- 10 Have returned to prewar position . 1
 Now on leave from permanent position 2
 Have made definite arrangements for a new position 3
 No definite prospect of employment, but expect to:
 Seek employment as a professional physiologist 4
 Get additional training in physiology before seeking employment 5
 Seek employment in another field 6
 Get additional training in another field before seeking employment . 7
 Retire 8
 Do not know 9

6 If you were to be identified with only one field of professional work, which of the following do you choose? Your choice may be independent of present affiliations. The purpose of the question is to present as far as possible, an overestimate of the number of physiologists relative to the numbers in related fields

- 11 Physiology 1 Anatomy 4 Medicine 7 Other 0
 Pharmacology 2 Biophysics 5 Surgery 8
 Biochemistry 3 Pathology 6 Zoology 9

7 Teaching

a Do you teach formal classes in

- 12 Physiology only? .. 1 Other subjects only? .. 3
 Physiology and another subject? ... 2 Or have you no teaching duties? .. 4

b In column I of code numbers below, circle the number representing the type of students to whom the major portion of your teaching time in physiology is given In column II indicate any other type of students to whom you teach physiology:

- | | I | II | | I | II |
|----------------------------|---|----|--------------------------------|---------------|---------------|
| 13 Do not teach physiology | 0 | 0 | Agricultural | $\frac{1}{4}$ | $\frac{1}{4}$ |
| 14 Graduate students | 1 | 1 | Non-professional undergraduate | 5 | 5 |
| Medical | 2 | 2 | Other (specify) | 6 | 6 |
| Dental | 3 | 3 | | | |

DECLARATION PROCEEDINGS

- 15-16 Is your teaching (of all subjects, including physiology) distributed over the entire calendar year or do you have intervals free from scheduled teaching? In each line below circle the number representing the number of months you had free from teaching in the years indicated: 1940 0 1 2 3 4 5 6 7 8 9 10 11 12 1945 0 1 2 3 4 5 6 7 8 9 10 11 12
- 17-18 d If you have teaching duties in your present employment, are conditions reasonably satisfactory for efficient teaching? Yes 1 No 2
- 19 e Which of the following do you consider the most serious handicaps in your teaching?

	Most serious	Next most serious
	0	0
	1	1
	2	2
	3	3
	4	4
	5	5

20-21 10 serious difficulty of any kind
Too many hours of teaching required
Classes too large for staff
Lack of physical equipment
Lack of technical help
Other difficulty not listed above (specify)

22 f If our present duties include research work, are conditions reasonably satisfactory for the carrying on of research? Yes 1 No 2

- 23-24 b Which of the following do you find to be the most serious of the difficulties you encounter in the carrying on of research?

	Most serious	Next most serious
	0	0
	1	1
	2	2
	3	3
	4	4
	5	5
	6	6

23-24 10 serious difficulty of any kind
Too much time required for teaching
Too much time taken up by other duties
Lack of physical equipment
Lack of technical help
Your own training not suited to the type of research you are doing
Other difficulty not listed above (specify)

- 25 g a Are you a member of the American Physiological Society? Yes 1 No 2

- b If a member, circle the number below representing the year (to nearest year) at which you were elected to membership:

21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	60 or over
41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60 or over	

26-27

- 10 Marital status and dependents

- a Are you: Unmarried? 1 Married? 2 A widow, widower or divorced? 3

- b Number of children (circle figure) 0 1 2 3 4 5 6 more

- c Total number of dependents: 0 1 2 3 4 5 6 7 more

- 29 30 11 Sex Male 1 Female 2

- 31 12 Income and rate of earnings

a Under "Total income" below, circle the code numbers corresponding to the income brackets which include your total income from all sources (before deductions for taxes, etc.), for 1940 and for 1945. Under "Professional income" indicate similarly the combined amounts of your salary, fees and other remuneration for professional work only for the same years. The object of this question is to ascertain in what degree physiology is a self-supporting profession.

	Total income	Professional income only	Total income	Professional income only
	1940 1945	1940 1945	1940 1945	1940 1945
32-33 No income at all	00 00	00 00	\$4000 to 4399	13 13
Less than \$1150	01 01	01 01	\$4400 to 4799	14 14
\$1150 to 1339	02 02	02 02	\$4800 to 5199	15 15
\$1350 to 1549	03 03	03 03	\$5200 to 5799	16 16
\$1550 to 1749	04 04	04 04	\$5800 to 6399	17 17
\$1750 to 1949	05 05	05 05	\$6400 to 6999	18 18
\$1950 to 2149	06 06	06 06	\$7000 to 7999	19 19
\$2150 to 2349	07 07	07 07	\$8000 to 8999	20 20
\$2350 to 2549	08 08	08 08	\$9000 to 9999	21 21
\$2550 to 2799	09 09	09 09	\$10000 to 12499	22 22
\$2800 to 3199	10 10	10 10	\$12500 to 14999	23 23
\$3200 to 3599	11 11	11 11	\$15000 or over	24 24
\$3600 to 3999	12 12	12 12		

b What part of the amount reported as professional income for 1945 was derived from work you did as a professional physiologist?

40 All 1 90 to 99% . 2 50 to 89% . 3 Part, but less than 50% .. 4
None 5

13 Rank or title.

41 a Are you employed in an institution using academic titles? Yes 1 No .. 2

b Circle the code number below indicating the rank or title you held in 1940 and in 1945.

	1940	1945		1940	1945
42 No academic title	0	0	Associate professor	5	5
Assistant	1	1	Professor	6	6
43 Instructor	2	2	Professor and department head	7	7
Associate or research associate	3	3	Dean	8	8
Assistant professor	4	4	Other (specify)	9	9

c Under each of the following years circle the code number indicating whether you were in a department of physiology or in another department in that year:

	1940	1945
44 In a department of physiology	1	1
45 In another department or field	2	2
In none	3	3

14. Are there provisions in your present employment for retirement with pay or with an annuity?

46 Yes . 1 No . 2

Part II

If your answers to any of these questions requires more space than is provided, use extra sheets

1-4 1. Name (print or type) _____
Last First Middle

5-6 2 Place and date of birth _____
7-8 State or province Country Month Year

9 3 Present address (at your place of employment, or your home address if unemployed)

10-11 _____
Number and street City State or province Country

12 4. Position held at present Give your rank or title and name of employing institution

13 _____
14 Title Institution

5 In your present employment, what percentage, roughly, of your working time is given to each of the following? Circle the nearest percentage figure in each line:

15-16 Teaching	0-5-10-15-20-25-30-40-50-60-70-80-90-100%
17-18 Research	0-5-10-15-20-25-30-40-50-60-70-80-90-100
19-20 Administration	0-5-10-15-20-25-30-40-50-60-70-80-90-100
21-22 Other duties	0-5-10-15-20-25-30-40-50-60-70-80-90-100

6. Teaching

a. Tabulate below the courses in physiology in which you teach, and the number of instructors (yourself included) participating concurrently in each course:

	Title and general subject-matter of course	Semester hours	Number of students	Number of instructors
23				
24-25				
26-27				
28-29				

b If you teach physiology, what criticism or comment do you offer on methods or subject-matter now in vogue in your particular field? Or,

c. If you teach another subject for which physiology is a prerequisite (e.g., pharmacology, clinical medicine), what criticism or comment do you offer on the adequacy of the students' preparation in physiology?

7 Are there any of your associates who might properly be classed as professional physiologists, but who are not listed in American Merit of Science or members of the American Physiological Society? If so, kindly write their names and addresses below:

8 The committee and the Council will welcome expressions of opinion on any matters dealing with the advancement of physiology. Have you any ideas to present on improvement of publication facilities, on meetings on employment services, on new fields of employment that might be opened to physiologists, on the obligations of physiologists to society, or on any other pertinent topic not specifically covered in our questions?

a Budget

a Indicate below the annual combined amounts of all funds that supported work in physiology for which you were administratively responsible in 1943 and in 1945. If your unit includes more than physiology, report only that portion of your funds that can be credited to physiology alone. Try to arrange that the funds listed by you will not be included in reports made by any of your colleagues. Following each year are lines of numbers representing multiples of \$1000, \$10000, and \$100. Circle one number in each line so that your budget is indicated to the nearest hundred.

30-33	1940	0 1 2 3 4 5 6 7 8 9	x \$10000	1945	0 1 2 3 4 5 6 7 8 9	x \$10000
		0 1 2 3 4 5 6 7 8 9	x \$1000		0 1 2 3 4 5 6 7 8 9	x \$1000
34-37		0 1 2 3 4 5 6 7 8 9	x \$100		0 1 2 3 4 5 6 7 8 9	x \$100

If your funds exceeded \$70,000 write the amount: 1940 _____ 1945 _____

b Of the totals reported in 9 a, what percentage approximately was devoted to (a) salaries paid to personnel; and salaries excluded, to (b) teaching and (c) research? Circle the appropriate percentage number in each line below:

38-39	Salaries, 1940	0-5-10-15-20-25-30-40-50-60-70-80-90-100
40-41	1945	0-5-10-15-20-25-30-40-50-60-70-80-90-100
42-43	Teaching, 1940	0-5-10-15-20-25-30-40-50-60-70-80-90-100
44-45	1945	0-5-10-15-20-25-30-40-50-60-70-80-90-100
46-47	Research, 1940	0-5-10-15-20-25-30-40-50-60-70-80-90-100
48-49	1945	0-5-10-15-20-25-30-40-50-60-70-80-90-100
50-51	Other, 1940	0-5-10-15-20-25-30-40-50-60-70-80-90-100 (specify)
52-53	uses, 1945	0-5-10-15-20-25-30-40-50-60-70-80-90-100

c Of the totals reported in 9 a, what percentage for each year was made up of short-term grants? (The remainder will be presumed to be continuous available from year to year). Circle the number representing the nearest per cent:

54-55	Short-term grants, 1940	0-5-10-15-20-25-30-40-50-60-70-80-90-100	of total reported
56-57	1945	0-5-10-15-20-25-30-40-50-60-70-80-90-100	

10 Personnel

a How many salaried persons other than technicians do work in physiology under your direction at present (1945)? Circle the appropriate number in each line below:

58	Number engaged in full-time research	0 1 2 3 4 5 6 7 8 9 10	more
59	" " " teaching and research	0 1 2 3 4 5 6 7 8 9 10	more
60	" " " teaching only	0 1 2 3 4 5 6 7 8 9 10	more

b How many students, excluding those who only attend normal courses, now work in your unit?

Major _____ Minor _____ Total _____

c Are your technical helpers adequate in number and quality? Yes 1 No 2

d If not in the deficiency, due to lack of available trained personnel, or to lack of money, with which to pay technicians?

68	Lack of available trained personnel	1	Lack of both	3
	Lack of money	2	Other difficulty (specify)	4

e What comments do you offer on the quality and number of advanced students and research workers available?

elected to its rolls. It is a young Society, since less than one-fifth of its elected members have yet died or resigned.

The membership has always included many persons who had affiliations with other sciences than physiology. Of the original 28 members, 43 per cent had titles in physiology. During the past 30 years the proportion of those having such titles, as recorded in the Yearbook list of members, has been constant at 37 to 38 per cent of the membership.

Another index to the development of physiology in recent years is furnished by the annual lists (Trotter et al.) of doctorates granted in physiology. The listing of such degrees largely depends upon the recognition by the educational institution of physiology as a department or as a field of study. Actually only half of those professional physiologists who hold doctorates other than M.D. obtained them in the field of physiology, as indicated both by the returns of the questionnaire and by checking the names of those to whom questionnaires were sent against the names listed under the doctorates in physiology.

In the years 1912 to 1945, the lists show 1274 doctorates in physiology in the United States and Canada. Their number increased with each pentad until 1941. In the years 1937 to 1941 the number per year was 75. During war II the number diminished steadily to only 25 in 1945, this diminution constitutes one measure of the present and future deficit of physiologists.

During the decade 1935 to 1944, doctorates in physiology constituted 2.5 per cent of all doctorates other than M.D. Degrees in the sciences furnished about half of all doctorates, and those in the biological sciences about half of the doctorates in all sciences. Therefore degrees in physiology are 10 per cent of the doctorates in the biological sciences. It seems evident that physiology is receiving a creditable share of academic recognition.

While the criteria according to which a particular doctorate is classified inside or outside of physiology are unsatisfactory, the total count of doctorates in this subject appears to be a useful number. The total number of professional physiologists who either belong to departments of physiology or now style themselves as physiologists is apparently less than the 1274 persons who have started from this field in the last 35 years. Therefore it is safe to conclude that physiology as recognized in the granting of degrees contributes more persons with doctorates to other fields than it receives from them.

It is now possible to visualize the composition of the present population of physiologists. From it a partial estimate of the future population can be gained. In Figure 3 are represented the numbers of persons who entered physiology and related

sciences in each 5 year period, from among 900 individuals who returned questionnaires. It may be assumed that those who belong outside physiology about equal insiders who did not answer the questionnaire. Thirty years earlier these same 900 were born. Thirty-five years later they will retire, since only a small percentage will die before the age of 65 years. Elections to membership in the American Physiological Society, based upon about the same number of persons, follow the same pattern through the years.

Conclusions to be noted are that a great acceleration in rate of entrants into physiology occurred after war I, and that acceleration ceased about ten years ago. Rate probably declined in the past five years, even though a small correction be made for the entrants not yet listed, from the

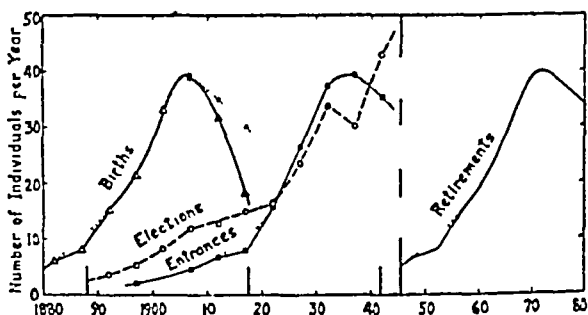


Fig 3 Rates of change in numbers of physiologists in North America. Births include 900 who answered the questionnaire, with suggested correction in later years for those not yet recognized as physiologists. Elections refer to membership in the American Physiological Society. Entrances represent answers to question 3 of the questionnaire. Retirements are placed 65 years after births. The early depression in each curve relates to war I.

known small lag in rostering those who enter the sciences.

A large block of physiologists are now 40 to 50 years of age. For the first time in history there are 4 or 5 individuals of this age group alone for each department of physiology.

If the population of physiologists becomes static, then less than the accession of 40 persons per year will be possible, for new places will be available only as deaths and retirements make room. The present median age of 40 years will gradually increase up to 46 years, half way between the age of entrance (28 years) and the age of retirement (65 years).

If, however, the population of physiologists continues to increase, then perhaps eventually as many as 100 individuals per year will be recruited into physiology, and a population of even 4000 physiologists may be realized within 50 years.

The effect of war II upon the numbers of physiologists will be estimated differently according to each estimate of future population trend. It seems certain that the number of entrants has fallen off during the pentad 1911-15. Already about 150 fewer doctorates in physiology have been given than in 1936-40. If, as the Bush report (1915) indicates, the effect of war II will continue for ten more years, the deficit of entrants to physiology may reach as high as 600 individuals. This figure is arrived at by noting that physiologists receive 5 per cent of all doctorates in the sciences, and accepting the Bush estimate of the

probable deficit of personnel about to be realized in all the sciences.

SUMMARY The status of physiology in North America is studied by use of data about individual physiologists. The present position represents a point in a historical continuum of teaching and research. The questionnaire of the American Physiological Society is described. From it and other sources the age distribution of present professional physiologists is obtained. Information regarding numbers of working physiologists, their training, their economic welfare, and their careers and incentives, are given in subsequent sections of this report.

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SECTION II THE IDENTIFICATION AND ANALYSIS OF THE NORTH AMERICAN POPULATION OF PHYSIOLOGISTS

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General considerations The most outstanding attribute of the "population of physiologists" is its unmistakable heterogeneity. This is so marked that the two operations indicated in the above title are very closely interdependent. The complexities of this situation color the conclusions and statistics presented, and demand therefore a discussion of its background and implications.

Those who regard physiology as a branch of biology naturally seek among biologists for students of the functions of living material, and may only grudgingly admit the "applied physiologists" who limit their interests to human physiology and its importance in medicine. On the other hand, those who hold physiology to be one of the "medical sciences" seem to regret that their cousins across the tracks have a right to the same

name, and they would encourage such distinctions as "physiological zoologist" and "plant physiologist." It should come as no surprise that the child of such jealous parents, growing healthy appendages only to lose them by fission, turns out to be an analytical problem.

As a starting point, the individual scientist might be expected to know, or at least to decide, what professional tag he should wear. But taxonomy on the basis of classes which are not mutually exclusive necessitates decisions which are either arbitrary or capricious, either leads to confusion. The processes, phenomena, and functions which are said to be the province of physiology are abstractions which cannot with any meaning be divorced from the living material in which they occur, some-

times not even from the kind of tool used to elucidate them. Thus there are independent parallel classifications of workers according to training, according to organism or organ studied, and according to purpose or viewpoint. Consequently the taxonomy of physiological scientists is in general not an "either or" problem, most of them have equal rights to at least two or three professional labels—occasionally even a fourth if they earn their living by teaching courses with titles not directly reflecting their research interests. (As will appear later, the situation even affords many the variety of an occasional change.)

This freedom becomes significant in the unmistakable tendency of workers in the physiological sciences to choose labels which emphasize their mutual differences rather than their similarities and the identity of their goals. The labels of related and component fields confess community of interest either not at all or by a mere adjective as in cardiology, neurology, endocrinology, nutrition, physiological chemistry, physiological psychology, physiological zoology (neurophysiology being an admirable exception).

This is in sharp contrast to the chemical profession, where there is constant emphasis on unity by such means as the labels biochemist, petroleum chemist, physical chemist, textile chemist, rubber chemist, analytical chemist, and so on (the one important exception is kept carefully tethered in the joint professional title "chemistry and chemical engineering"). They all belong to the same society, 33,000 of them, they attend large or small meetings under the auspices of that one society, and they are further held together by their excellent and comprehensive journals, particularly "Chemical Abstracts." The interests of the biochemist may actually be closer to those of the endocrinologist than to those of the petroleum chemist, but in name and professional loyalty the tendency is in the opposite direction.

This situation reflects both strong and weak aspects of physiology as a science and as a profession. Without question, a large share of the vigor of physiological research and the acceleration of its progress have been due 1) to its success in recruiting and inspiring the possessors of all manner of specialized tools, skills, and techniques (e.g., surgical, physical, chemical, electrical), 2) to the intensive forays of determined small bands in restricted fields, and 3) to the constant goad of a demand for the solution of particular problems for progress in the healing arts.

If the valued representatives of these three influences prefer not to become nominally amalgamated (even in some cases to secede), acquiescence may seem an unimportant concession, but the formation and maintenance of the most useful groups and programs for optimal scientific inter-

change and mutual inspiration—goals of true professional unity—are thereby rendered much more difficult and uncertain. The present attempt to identify the population of physiologists in a useful way is a case in point. The presence of both physiological and non-physiological workers in all the nominally dissident groups poses problems to which the available long distance methods could scarcely give completely satisfactory answers. We believe that the inclusion of the one fraction is just as essential to the picture as is the exclusion of the other, and that the corresponding statistical limitations should be constantly and stringently observed.

Evaluation of source materials. Since the committee knew of no personnel surveys which had been conducted with precisely the present goal, it settled on the sources of information that seemed to offer promise of the most material in usable form. The abnormal frequency of professional and geographical dislocations has accelerated the obsolescence of data published even since 1943, but while a better job could be done in normal times only a few important aspects of a rough outline seem seriously distorted by this shortcoming.

a. *The seventh edition of the "Biographical Directory of American Men of Science"* was published with a preface dated February, 1944. Compilation and publication had taken time; this reporter's information was requested in April, 1942, but some entries carry changes dated as late as 1943. The list is not a census solicitation of names and data is thorough but both are voluntarily supplied. The emphasis is admittedly on investigative science, which practically limits the original selection to doctors (whatever they may do later). Such a limitation is thus impressed on any roster based on this list.

The coverage of biological scientists and medical research workers seems good, though naturally less complete at the lower age levels. For example, entries were found for 90% of the members of the American Physiological Society, for 77% of the doctors in the physiology division of the National Roster, and for 67% of the list of doctorates in physiology to be described, a third of the remainder being of 1940 or later.

Fortunately the editing is excellent, as all users of the book know, and within the limitations of space and the cooperation of those listed there is a very satisfying wealth of well-chosen material. For the present study, the chief item whose absence was keenly felt was the field or department of the doctorate. Considerations of the apportioning of available time have precluded the codifying and analyzing of more than a small portion of the information furnished by "American Men of Science."

b. *The national roster of scientific and specialized*

personnel offered a listing of physiologists designed to furnish, especially for war purposes, information on training and skills, already tabulated and coded for machine analysis. Little biographical material had been collected, however, and certain other definite limitations were inherent in its purpose and methods.

For the present study its coverage suffers from the deliberate exclusion of the medical profession, only two of the 100 doctorates counted are classified in medicine. Another exclusion results from the seeding of the physiologists and biochemists in different major divisions, namely "biological and agricultural sciences" and "chemistry." There is little provision for the chemical physiologist in the former group except in a small sub-subgroup with the catch-all designation, "digestion, metabolism, and excretion."

Coverage by the National Roster is further limited by the part of its purpose directed toward draft deferment of essential scientists, doubtless those so affected have felt more stimulated to cooperate in keeping their files up to date. However, while its horizontal spread is thus narrowed, its vertical depth is greater than that of "American Men of Science", with over 200 names of non-doctors. An additional admirable feature is its continuing attempt to attract new registrants in the lower educational brackets and to keep abreast of changes by periodic rechecks.

The published totals of the National Roster put 857 in the physiology classification, (December 1944), the material sent to the committee actually listed 828 names (December 1945). Of these, 214 were set off separately because only preliminary data had been furnished, subsequent questionnaires not being returned. The machine tabulations used by the committee are based on only the 614 with complete data. A further limitation lies in the lack of addresses: the necessary ones were furnished, but too late for inclusion in our original mailings. The preliminary, non-mechanical, analytical studies are based on the 549 from the 828 for whom addresses and titles were found, either in "American Men of Science" or in the Federation Directory. Thus the three different samples used may bear slightly different kinds of bias, but the extent of this is not known.

c *Annual listing of "Doctoral Dissertations Accepted by American Universities"* offered the best known chance to investigate the rate of production of physiologists. From this series all the degrees granted in physiology from 1920 through 1945 were compiled, and the present writer correlated the results with those from the other sources. Here again, however, purposes and definitions different from those of the present study imposed most stringent limitations on the significance of the counts.

The chief source of confusion lies in the variety of meanings of the "doctorate in physiology" at different universities. Some give the degree only for work done in a medical school department of physiology, while others recognize physiological research done in a department of biology, a department of botany, or a school of agriculture. In some graduate schools several departments are combined as "Physiological Sciences" and their biochemists and pharmacologists all appear among the physiologists. As was pointed out in the preceding section, such inclusive classifications have a real significance, but comparisons with the narrowly defined group necessarily treated in the present study are hazardous.

d *Replies to the committee's questionnaire* are superior to all other sources in two respects: they furnish answers to specific questions asked for the purpose of this study, and the data are recent. However, some limitations must be kept in mind too.

The total number of replies is gratifying, but the groups in some classifications are too small to be regarded as significant. As an extreme case, one reply from Nevada puts that state high in the ranking of per capita endowment with physiologists.

The individual limitations of the material used to compile the mailing list, so far as they do not completely offset each other, are inevitably impressed on this source as well.

The statistics describe a population already selected according to the arbitrary criteria listed in the introduction to this report. Also, the degree and character of the selection represented by willingness to answer the questionnaire are unknown but perhaps not negligible factors.

Unavoidable compromises between the open and confidential parts of the questionnaire, a few unforeseen complications, and occasional misunderstandings of questions have detracted from the value of some of the statistics.

e *A few miscellaneous sources* have contributed small items to the study. The additional names suggested on replies to the questionnaire may or may not represent the kind of "physiologist" defined for this study, but they were circularized too late to cause any distortion of the counts available for report.

An attempt to analyze the physiology departments of medical schools gave only very rough figures because of the variable designations of positions, the combinations of departments with pharmacology, biochemistry, nutrition, and hygiene, different treatments of wartime vacancies, and the widely varying age and completeness of the available bulletins and catalogs.

Population figures are those of the 1940 U. S. census. Data on medical schools and medical

students are from the annual survey (1945) by the Council on Medical Education of the American Medical Association

Analytical studies and results a Self-classification After acceptance of the membership of the American Physiological Society ex officio, the first criterion for identifying a definable population of physiologists was self classification. The form in which this question is put to a worker is clearly one determinant of the answer received. The italics immediately following the name in an "American Men of Science" entry are obviously intended as a coarse screening into broad scientific groups. However, the blank on which the data are submitted actually asks at this point for "subject of investigation—e.g., physical chemistry", and a scientist can hardly be blamed for a desire to identify himself with as specific a field as he believes he fits. He is presented with an unlimited choice and the tendency toward differentiation would seem to be encouraged. In the breakdown of such classifications, some arbitrary decisions were necessary. Confronted by workers who identify themselves with "hemodynamics", "metabolism", "genetics", "endocrinology", "nutrition", "physiological chemistry", the analyst must choose between a mulish adherence to the fetish of the word *physiology* and a personal opinion which he hoped to submerge as deep as possible in complete objectivity.

The National Roster check list asked for identification with a "principal professional field". It offered some 26 choices in the biological and agricultural sciences, including (besides physiology) pharmacology and experimental therapeutics, bacteriology and immunology, anatomy, pathology, plant physiology, biology, zoology, genetics, and nutrition—but not including medicine or physiological chemistry. The list received by the committee consisted of all who had first chosen "physiology".

The committee's questionnaire asked for identification with a single "field of professional work" regardless of present affiliations, offering the following choices: physiology, pharmacology, biochemistry, anatomy, biophysics, pathology, medicine, surgery, zoology, other.

Individual inspection of the 34,000 entries in "American Men of Science" yielded 900 self-styled "physiologists". 500 members of the American Physiological Society and 400 non-members.

All 828 National Roster names represented self-styled physiologists, but only 550 of them were found in "American Men of Science" and could be used for comparisons and for the first mailings. Of these, 390 had been consistent in their designations, being listed in physiology in both sources, 160 had given different answers to the two questions, while the Roster had failed to register by

first choices 350 of the self-styled physiologists present in the book.

The combination of these two sources gave a total of 1,060 scientists who at one recent time or another had classified themselves in the field of physiology. This group thus represented 70% of our mailing list of 1,500. One of the few gross discrepancies between the questionnaire statistics and the preliminary analysis showed up when only 52% of the replies gave their choice as "physiology". If this is a sampling error it represents a very extreme selection in a direction opposite to what was thought likely. The alternate conclusion is that one third of those who, two to three years ago, considered themselves physiologists have either shifted to another field or changed their minds about where they should be counted. Either of these situations might be of interest. The separation of the confidential fraction of the questionnaire precluded comparisons which would decide between them.

b Declared researches The "subjects of research" listed at the end of each entry in "American Men of Science" permitted an estimate of the number of scientists who might reasonably be classed as physiologists according to a broader definition than that used for the core of this study. In addition to the primary roster of physiologists for the mailing list, a second file has been constructed to include workers in component fields not formally termed physiology, as well as genuinely physiological workers in related fields. This classification would follow quite closely the criteria for election to the American Physiological Society, except for lack of information on the quality of the research or on the continuity of interest in the field. The aim of our selection has been to distinguish, for example, between the physiologist and the chemist in biochemistry, between the practising physician and the research workers who both label themselves endocrinologists, between the organic chemist and the physiologist in pharmacology, between the surgeon and the physiologist in neurology, between the electronics technician and the physiologist in biophysics, between the clinician and the student of growth, development, and metabolism in pediatrics, between the general biologist and the physiologist in genetics, between the scientific farmer and the endocrine physiologist in dairy and poultry husbandry, between the dietician and the physiologist in nutrition, between the psychometrist and the sensory physiologist in psychology.

This file is probably not complete, as the necessary judgments were more time-consuming than those for the primary group (Inclusion often had to be based on a quick personal reaction to the researches listed). Nor has time yet permitted

the analysis of the population represented. There are approximately 1,400 cards in the file (almost as many as the original mailing list) and the above examples are taken from a cursory inspection of the categories represented. Many of the workers listed would admit to being physiologists if asked in the right way (some of them have actually done so) and many more either have been or well might be deemed true physiologists by their colleagues (witness many of the names suggested on returned questionnaires). There is probably some dead-wood here too, but the writer believes that a knowledge of the approximate size of this group may be useful as a corollary to the more intensive study of the narrower group.

Finally, there is at hand an unsorted pile of about 700 to 800 entries. Its formation was dictated primarily by a profound disinclination to have any late change of criteria require another screening of "American Men of Science." Another reason was the recognition of unavoidable changes of policy or mood from day to day in making the original selections. Plant physiologists comprise the only consistent group in this pile, the rest are mostly borderline cases, and shifts back and forth between them and the secondary file may develop if further analysis seems worthwhile.

The inclusion of the plant physiologists in this last group should not be taken to mean that the writer regards them as any the less physiologists. There is, however, a rather widespread feeling that their interests are more closely related to other botanical studies than to other physiological studies (although the terminology of the U. S. Civil Service and the classifications of the National Roster imply a dissenting opinion).

c Employment as physiologists. The "American Men of Science" entries disclosed 616 scientists who held titles in physiology. This number includes several whose employment was interrupted by military service, and a few who had graduated to "emeritus" or administrative levels. On the other hand the data do not permit a distinction according to academic department: an instructor in physiology in a college biology department falls in this group, but not necessarily a professor of biophysics or optics in a department of physiology.

Only 65 of this group did not classify themselves as physiologists in either "American Men of Science" or the National Roster or both. It should be noted in this connection that almost this same number (55) of the members of physiology departments represented in the replies to the questionnaire called themselves non-physiologists.

The percentages of titles in physiology and of members of physiology departments (36% and 38% respectively of replies) did not differ significantly from the 41% represented by the 616 in the total mailing list.

d Distribution of physiologists. The geographical and institutional distribution of physiologists cannot fail to reflect in some measure the criteria accepted for their definition. The main outlines of the picture, however, are probably given by the questionnaire replies without unfair distortion. It is not surprising to find two thirds of the physiologists working in universities, the rest are about evenly scattered among five kinds of employment: other teaching institutions, research institutes, commercial laboratories, government services, and hospitals.

Such specialized educational and research services are not equally apportioned to the general population, and physiologists follow an extension of the same rule. Five of the most populous states (New York, Pennsylvania, Illinois, California, Massachusetts) have about a third of the national population and a third of the country's medical schools. The schools, however, are among the largest and have 42% of all the medical students. Their physiology departments in turn are disproportionately larger, employing about half the country's medical school physiologists. Undoubtedly this is an important factor in the receipt of 45.5% of the questionnaire replies from these five states. At the other end of the scale, three of the five states which sent no replies (Maine, Idaho, New Mexico) have no medical schools.

e Statistics relating to age, training, and achievement, and growth of the profession. A satisfactory analysis of the available figures would require more actuarial experience than the present writer can claim. Overall population and economic trends, the increase in higher education generally, expansion of medical teaching and elevation of its standards, the interplay of applicable theoretical and technical advances in physics and chemistry, increasing financial support for both pure and applied research from public, philanthropic, and industrial sources—all these must have played significant roles, and the questionnaire data are scarcely numerous or varied enough to justify numerical distinctions among the factors at work.

The replies to the questionnaire came from physiologists whose median birth year was 1905, with nearly 60% of them between 1900 and 1915. 82% of them were born in the United States, three quarters of these in the northeastern and mid-western states.

They earned Ph.D. degrees or otherwise considered themselves to have entered the profession about the median year 1932, with roughly 60% between 1928 and 1942. The annual entrances climbed slowly until the late 1920's, increased suddenly to a rate that was steady except for a spurt in 1939, which was followed in 1942 by a very sharp decline.

About 77% of this group took a Ph D (or Sc D) degree, 36% an M D, with 19% holding both, and approximately 57% of the Ph D degrees were taken in physiology. Roughly 60% of their Ph D degrees probably came from ten universities.

They had, on the average, from one to two years of post-doctoral training of some kind. Those who have academic titles scatter about a median at about the associate professor level. The median age of election for present members of the American Physiological Society is 32 years.

The replies received indicate that the Society is fairly representative of the group studied. The proportionality between members and non-members showed only insignificant variations through most of the comparisons, except for a slightly higher fraction of non-physiological teaching and extra-university affiliations among the non-members.

Conclusions As indicated earlier, identification of the individuals comprising the group of North American physiologists is handicapped by dispersive practices in terminology. Emphasis, in self-classification, upon the animal, the organ, the tissue, or the function studied, upon tools or training, and upon the formal names of departments and courses, makes quite arbitrary the characterization of some fields as components of physiology, others as related to physiology. It is true that two lists have been compiled: a primary file of some 2,000, identified principally through their professed adherence to the name of physiology in some connection (though only about 250 meet simultaneously all the criteria), and a secondary file of some 1,400 who seem from records of their research to deserve a place in the profession. But

such distinctions are most artificial, with boundary diffuseness differing only in degree.

This argument may strike many as trivial and far from startling, but it is a salient aspect of "the status of physiology" which this committee was asked to survey. It is also fundamental to the choice of policies designed "to promote the advance of physiology." For the interests of "teachers of physiology" might best be served by one policy, those of "medical physiologists" and "physiological biologists" possibly by quite antagonistic policies. Interests common to the group of self-confessed physiologists (many only for want of the more specific tags used by others) are more difficult to identify. And separatist tendencies have left the broad field of biological function with very little clearly focused evidence of its community of scientific interest.

The statistics quoted above suggest that this last-mentioned trend is a progressive one, and it is a source of regret to many. Much of it has passed the reversible stage, but physiology as a science and as a profession could profit from efforts to reawaken a recognition of the mutual interdependence of manifold branches of endeavor. Retention of unity in name is suggested as one promising kind of binder. To this end, labels for courses, departments, titles, societies, and fields of study, which emphasize their essential nature as parts of physiology, are strongly advocated.

It is a pleasure to acknowledge the indebtedness of the writer and the committee to Miss M. K. Reiser, without whose painstaking and resourceful assistance the compilation of the rosters described would have been a well-nigh insurmountable task in the available time.

SECTION III ECONOMICS

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The questionnaires returned give data on the economic situation, in 1940 and again in 1945, of the group addressed. The first of these years was a time of peace for the majority of North Americans. The second brought the end of the war and the beginning of postwar readjustment. Presumably there was, during the interval between, an abnormal number of shifts in employment. The war no doubt also influenced the rate of pay and of promotion of those who did not change employers. It must have affected in some degree the age distribution of the group. But we have no data, covering a comparable period of peacetime, for

comparison. Incomes received by the group in 1940 will be compared with those received in 1945, but such comparisons are hardly valid unless due correction is made for the reduced purchasing value of the currency unit in the latter year. To compare incomes of 1945 with those of 1940 requires the use of a correcting factor which does not appear to have been authoritatively fixed. It must therefore be supplied by each reader for himself.

The group to which the questionnaire was addressed is, from the economic point of view, a heterogeneous one. Its members were not selected solely for the purpose of an economic study. They

have a common interest in physiology, but nearly half of them prefer to be identified professionally with some other biological science. Some of them are supported entirely by salaries which they receive for research or teaching, or both, in physiology, but among them are some whose incomes are derived from the practice of medicine or surgery, and who may, through indulging in active interest in physiological research, incur an economic loss rather than a gain. Many others occupy intermediate positions between these extremes. The connection between the individual's income and his work as a physiologist is thus highly variable. This is true even among those who choose physiology as their primary field of affiliation.

We shall therefore present only a few general statements concerning the entire group addressed, and give more detailed figures on some of its subdivisions.

1 *The entire group* The total number of returned questionnaires furnishing material for the present report is 955. On reading these, it became evident that the wording and arrangement of certain parts of the questionnaire had allowed some misinterpretation on the part of those answering. The question on the sex of the addressee (question 11) was placed in unfortunate juxtaposition to the question on marital status and dependents (question 10). The result was that in some instances at least the answer to question 11 gave the sex of the addressee's dependents rather than his own. This was obvious because (a) on several questionnaires the addressee, having dependents of both sexes, wrote in the number of each as the answer to question 11. (b) although this part of the questionnaire (Part I) was designed to be anonymous, a few individuals wrote in their names or other marginal notations sufficient for identification. Two of these answered question 11 in a way which the committee can best account for by attributing it to an error of the type described. We have no way of knowing how many unidentifiable persons, each with one dependent of the opposite sex, made a similar error. Of the 955 questionnaires 116, or 12 per cent, were marked as returned by women, the actual percentage of women in the group is probably somewhat lower.

Eighty six per cent of the entire group are married. The number of children per individual, for the entire group, averages 1.7, and of dependents 2.4. There is little or no correlation between income and number of dependents, if persons of the same age group are compared. Sixty-nine per cent of all answering have provisions of some kind for retirement with pay at their places of employment.

Five hundred thirty-nine (56 per cent of the group) remained at their prewar places of employ-

ment during the war years. Four hundred two (12 per cent) changed employment in one way or another (this figure includes some, but not all, of those who entered professional life between 1940 and 1945). Of the 102 who changed employment, 155 entered the armed forces, 151 changed to new civilian positions not in government service, 65 entered government service as civilians on full time, and 23 on a part time basis.

Nearly a third (312) of all who answered had entered some kind of temporary employment during the war, in the armed forces or elsewhere. The postwar employment prospects of these, as seen by themselves at the end of 1945, are shown in table 1.

Only 2 per cent (16) of all physiologists reported themselves as unemployed at the time of answering the questionnaire. Demobilization of the

TABLE 1
Employment prospects of those who were employed in temporary positions during the war

Returned to prewar position	109
Now on leave from prewar position	25
Have definite arrangements for a new position	63
	197
Will seek employment in physiology	57
Will seek employment in other fields	18
	75
Will seek additional training in physiology	6
Will seek additional training in other fields	15
Expect to retire	7
Do not know	12
	40
Total	312

armed forces was then in progress, the unemployment figure might have been even less if the questionnaire had been sent out a few months earlier or a few months later.

About 15 per cent of the returned questionnaires withheld any information on incomes, and some of the others gave only partial answers. Increase of professional income by at least one bracket, between 1940 and 1945, was reported by 80 per cent of those answering. Sixteen per cent remained stationary. 4 per cent regressed.

Income from non-professional sources contributes to the support of a small minority of the group, it goes mainly to those with relatively high professional incomes. Eighty per cent of those reporting for 1940, and 75 per cent for 1945, list professional income and total income in the same bracket. Of those who report outside income, at least two thirds in both years had professional incomes alone above the median level. This is true even though the brackets of annual income were

only \$200 or \$400 apart in the lower ranges, but \$600 to \$1000 apart in the upper ranges

Those who were in the armed forces during all or part of 1945 had understandable difficulty in answering question 12 on professional income for that year. Some of them omitted any answer, some circled the code number 00, indicating no income at all, some listed their service pay, while still others, on leave from civilian positions, listed the salaries they would have received if they had remained in them. The figures on income given in this paragraph exclude, as far as professional income for 1945 is concerned, all those who were in the armed services, they also exclude all income data for 1940 for those who list themselves as having entered professional life later than 1939, and all 1945 income data for those who list themselves as having entered professional life in 1945. With these exclusions, median annual total income for the entire group was \$3800 in 1940 and \$5050 in 1945. The median annual professional income increased during the same period from \$3700 to \$4700. Because of the confusion in answers to question 11, referred to above, the incomes of the women as a subgroup cannot be determined with certainty, but discarding those answers which obviously were erroneous, and taking the remaining returns without question, the median annual professional income of the women was \$2700 in 1940 and \$3200 in 1945. The age distribution of women in the group is not greatly different from that of the men. There is some difference in distribution of degrees, for example, 19 women (17 per cent of their total number) had no doctorate degree, as compared to 2 per cent of the men.

2 *Physiologists, self-classified as such*. In the questionnaire the addressee was asked to state his own primary professional affiliation, whether in physiology or in some other related field. We therefore have several subgroups, the largest being made up of those who classify themselves as physiologists, with smaller groups of those who belong primarily in medicine, biochemistry, anatomy, etc. It is not certain that the smaller subgroups constitute representative samples from the professional fields to which they primarily belong. Hence it would be useless, and perhaps misleading, to compare one subgroup to another in respect to income. At the same time the combined figures from all of the returned questionnaires cannot be taken as applicable to physiologists alone.

Of the 955 persons who answered, 52 per cent (497) classify themselves as physiologists. Table 2 shows the distribution of these according to degrees held.

In 1945 about three-fourths of the self-styled physiologists were employed in institutions using academic rank or titles, the majority in departments of physiology. The nature of employment

outside of academic institutions was not asked for specifically. The distribution is as follows:

Relation of income to length of professional experience. In the questionnaire those who held the Ph.D. or Sc.D. degree were asked to indicate the year in which it was awarded. Those holding

TABLE 2

Distribution of self-styled physiologists according to degrees held

M.D. and Ph.D. or Sc.D.	67	D.V.M. or D.V.Sc.	3
M.D. and M.S. or M.A.	29	M.S. or M.A.	31
M.D.	39	Bachelor	8
Ph.D. or Sc.D. (physiology)	229	Degree not stated	3
Ph.D. or Sc.D. (other)	88	Total	497

TABLE 3

Distribution of self-styled physiologists among academic and non-academic positions

	1940	1945
In departments of physiology	210	259
In other departments using academic titles	107	106
Retired	4	8
No academic title, or no answer	46	115
	367	488
Degrees conferred in 1945-1946		9
		497

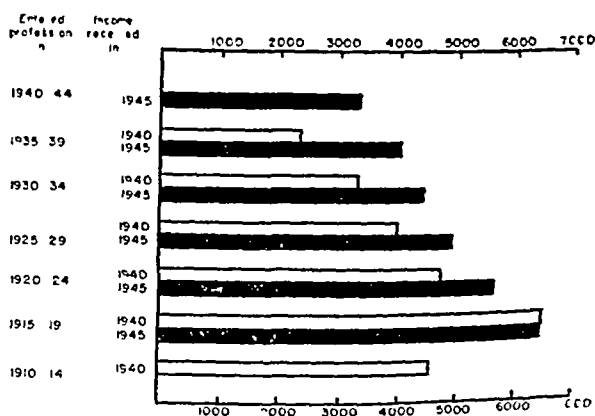


Fig. 1 Professional incomes (median), in 1940 and 1945, of those classifying themselves as physiologists. Shown in relation to year of entering profession.

neither of the degrees named were asked to indicate the year of entry into professional career. On this basis the self-styled physiologists were arranged into five-year groups, the youngest group being made up of those whose degrees were received, or who entered professional life, in the years 1940 to 1944 inclusive. The median annual professional income for each of these five-year groups, in 1940 and in 1945, is shown in figure 1.

No group containing fewer than 10 individuals is listed. The smallest group appearing (1910-11) had only 10 members in 1910, and had been reduced to 9 in 1915 by one retirement.

In figure 1 the increase of professional income between 1910 and 1915, shown for each of the younger groups is partly the increase of earnings normally to be expected from an added five years of professional experience. It is also in part due to change in the general economic situation, this effect may be roughly evaluated by comparing the 1945 income of each group with the 1940 income of the next older group. From such a comparison it appears that wartime conditions increased particularly the earning power of the younger people, this increase becomes smaller as successively older groups are compared. It is perhaps worth noting that the 1910-14 group, in 1910, had a lower median income than did the group of 1915-19. This fact might indicate that in peace time the peak of earning power is passed after 25 years of service, but in 1945 the 1915-19 group had exceeded 25 years and maintained the same level of income as in 1940.

3 *Holders of the Ph D degree in physiology* Of the 955 persons answering, 32 per cent (305) list themselves as having the degree of Ph D or Sc D in physiology, but not the M D. Six of these received their degrees in 1945. Of 299 with degrees conferred in 1944 or earlier, 15 per cent (45) were in the armed services. Seventy one per cent (213) held academic positions in 1945, most (122) in departments of physiology and fewer (91) in other departments. The nature of the employment of the remaining 14 per cent (41) was not specified. One might conclude from these figures that nearly all those who enter professional life with only the Ph.D degree in physiology find employment in academic positions. It should be noted, however, that the number of Ph.D degrees "in physiology" granted by North American universities since 1912 is more than four times the number of those holding such degrees who answered our questionnaire (see section 1 of this report). We have no way of knowing what became of those not listed here, nor can we be sure that we have a representative sample of the total number.

Considering the holders of the Ph D in physiology who are in academic positions, and comparing those in departments of physiology with those in other departments, the latter have, on the average, slightly higher academic rank and incomes. Their median annual professional income, for 1945, was \$4250, the median for those in departments of physiology, \$4050. But those in other departments are a slightly older group. The median year of their entry into professional life is 1934, as compared to 1936 for those in departments of physiology.

Of the 305 doctors in physiology, 77 per cent (236) now classify themselves as physiologists. The remaining 23 per cent (69) choose affiliation with other biological sciences, chiefly biophysics (20), pharmacology (15), and biochemistry (14).

1 *Those holding academic positions in departments of physiology* Of the 955 persons who answered the questionnaire, 36 per cent (346) report that they held academic positions in departments of physiology in 1940, and 34 per cent (327) in 1945. The titles listed in the questionnaire were department head, professor, associate professor, assistant professor, associate, instructor, and

TABLE 4
Academic ranks in departments of physiology, in relation to degrees held, 1940 and 1945

IN 1940	DIRECTOR 1	PROF 2	ASSOC. PROF 3	ASST. PROF 4	INSTR. 5	ASST. 6	OTHER 7	TOTAL
M D and Ph D (or Sc D)	13	4	9	11	7			46
M D and M S (or M.A.)	7	4	4	4	5		3	27
M D	13	2	6	7	9		1	38
Ph D or Sc D (other science)	8	7	12	13	11	1	2	54
Ph D or Sc D (physiology)	8	16	20	21	33	1	4	139
D V M or D V Sc	1	1		3				5
No doctorate	1				29	41	2	73
	51	36	51	59	94	43	12	346
IN 1945								
M D and Ph D (or Sc D)	16	11	8	9	5	1	2	52
M D and M S (or M.A.)	9	4	3	4	3		2	25
M D	15	3	5	9	4	1	3	40
Ph D or Sc D (other science)	11	10	10	14	10		2	57
Ph D or Sc D (physiology)	19	11	25	33	28		6	122
D V M or D V Sc	2	1	2					5
Nodocortate	1			4	9	10	2	26
	73	40	53	73	59	12	17	327

assistant. Titles not included among those named were put into a miscellaneous group of "other ranks." Table 4, below, shows the distribution of ranks according to degrees held. The two ranks of associate and instructor are combined in the tabulation, because the salary ranges for the two ranks were found to be approximately the same.

From table 4 it is evident that of the doctorate groups listed the holders of degrees in physiology occupy the lowest average rank. Their relative position improved somewhat between 1940 and 1945, but is still inferior to that of the other groups. The professional incomes of the doctorate

in physiology are correspondingly low, as is shown in table 5

In tables 4 and 5 the doctorate groups listed include, for 1940, only those who received the Ph D degree, or who entered professional life, in 1939 or earlier, for 1945, those who received the Ph D degree or entered professional life in 1944 or earlier

The relatively low ranks and incomes of the doctors in physiology do not necessarily mean that preference in appointments is given to holders of other degrees. The doctorate groups vary among themselves in average length of professional service. The doctors in physiology are a comparatively young group. The median year of receiving their Ph D degrees, and presumably of their entry into professional life, is 1936 (in the 1945 tabulation). For those holding doctorates from other sciences it is 1930. For those with the M D, alone or combined with a master's degree, the median year of entry into professional life is 1926. Among these groups, the differences of rank and income can be attributed mainly to differences in average length of service.

If any doctorate group holds an economically favored position with respect to preference in appointments, it is the group holding both M D and Ph D degrees. The median year for the award of their Ph D degrees is 1933, but of the 52 individuals listed in this group for 1945, 33 earned the M D after the Ph D. Hence for this group the median year of entry into the profession must have been some time later than 1933, and can hardly have been more than a year or two earlier than the median year (1936) for the holders of Ph D in physiology.

The relative age of the M D groups makes it evident that in recent years few young men with the M D alone have stayed in physiology. If they have entered the field, they have either secured the Ph D as additional preparation, or they have moved out. Those with the M D alone, if they elect to remain in physiology, apparently fare as well as those with the Ph D alone. Those with M D degrees have a somewhat greater freedom of choice whether to remain or not. The number of young men lost from physiology to other fields, and the reasons for their leaving, are discussed in section 4 of this report.

Professional income in relation to academic rank in departments of physiology. Only 2 of 43 persons listed as assistants in 1940, and 2 of 12 in 1945, held doctorates antedating those years. The assistants were evidently for the most part graduate students employed on a part-time basis. In 1940 their median annual pay was less than \$1150, in 1945 7 of the 12 reported more than \$1150. The small number of assistants reported for 1945 may be largely due to the reduced number of graduate

students available. But it is also probable that the sources from which our roster of physiologists was made up did not furnish a representation for the lower ranks in 1945 equal to that of 1940. No doubt this is true as far as assistants are concerned, in some degree it may apply to associates and instructors.

Those with miscellaneous academic titles grouped under "other ranks" numbered 12 in 1940, 17 in 1945. Their median annual professional income was \$2250 in 1940, \$1600 in 1945. In each of those years there were only two of the group who did not hold doctorates.

Table 6 shows the frequency distribution of professional incomes according to academic rank in departments of physiology, in 1940 and in 1945. The ranks listed are from associate or instructor (combined in the tabulation) to department head.

In table 6 it will be noted that between 1940 and 1945 the median income bracket shifted upward for assistant professors, associates and instructors, but remained stationary for the upper three ranks.

TABLE 5

Median annual professional incomes, 1940 and 1945, of those holding academic positions in departments of physiology, shown in relation to degrees held

	M D AND PH D	M D AND MASTER	M D ONLY	PH D OR SC D (PHYSI OLOGY)	PH D OR SC D (OTHER)
1940	\$4400	4300	4000	3300	3600
1945	5000	4950	5000	4050	4500

There is, however, some upward movement in each rank. The brackets are not uniform intervals, the extent of each bracket is only \$200 in the lower range, widening to \$400, \$600, and \$1000 at the middle and upper levels. Table 7 below shows the median professional income for each rank, calculated from the assumption that all units falling within the median bracket are evenly distributed over it. The table also shows the median number of years elapsed since entry into professional life (or date of Ph D degree), for the individuals holding each rank.

We do not know to what extent the changes of income between 1940 and 1945 represent actual increases of basic salary scales. The term "professional income" was used in the questionnaire to include all salaries, fees, and other remuneration received for professional work. Hence the amounts listed do not necessarily mean salary alone, though in most instances professional income from other sources is probably negligible. During the war some institutions temporarily allowed extra pay for extra duties assumed in connection with the war program. Finally, there was some depletion of institutional staffs during the war, and where the

local salary scale was low the loss of personnel may have been a high fraction. Hence low paying institutions may have relatively a larger representation in our figures for 1940 than in the figures of 1945.

The economic situation of the individual was of course improved in many instances by promotion in rank or by transfer to a different field. Table 8

rank. Of the 7 who were still without doctorates, all reported increases of income, though only 2 had been promoted.

Thirty five transfers from one department of physiology in 1940 to another in 1945 were reported. This figure includes those with and those without doctorates in 1940.

SUMMARY AND DISCUSSION Physiologists as a

TABLE 6

Distribution of annual professional incomes, 1940 and 1945, of those holding academic rank of or above instructor in departments of physiology

INCOME BRACKET	1940					1945				
	director 1	prof 2	assoc prof 3	asst prof 4	instr 5	director 1	prof 2	assoc prof 3	asst prof 4	instr 5
\$10000 or over	4					0	1			
8000 to 9999	1					4	1			
6000-7999	2	1				5	1			
4000-5999	6	2	1			9	4		2	
3000-3999	3	4				7	1	1		
2000-2999	11*	4	1			11*	6	4	1	
1500-1999	3	3	1			8	2	3	3	
1000-1499	9	5*	6	2		8	0*	8	3	2
750-999	2	5	7			6	0	6	4	2
500-749	3	3	10*	7	2	2	2	16*	13	5
350-499	1	1	7	10		2		9	13*	5
250-349	1	2	0	14*	8	1	1	4	21	8
150-249	3	1	6	11	5			1	12	14*
100-149			1	4	10					7
75-99		1		6	17				1	8
50-74				1	8*					
25-49				2	6					2
15-24		1			13	1				3
Below \$1750	1				19					2
No answer	1	3	2	2	6	3	3	1		1
Totals	51	36	51	59	94	73	40	53	73	59

* Median bracket for the rank and year indicated.

shows the number of promotions, transfers and new appointments, of all personnel with doctorate degrees, between 1940 and 1945. It should be noted that the table lists only transfers between physiology and other fields, not transfers from one department of physiology to another.

Practically all the promotions and transfers listed were accompanied by increases of income. Of the 98 whose rank remained unchanged between 1940 and 1945, 42 were department heads in both years, and 66 of the 98 reported increases of income by at least one bracket. Of the 4 demotions, 2 were transfers to new positions at lower rank but higher salary, only 1 of the 4 transfers entailed a reduction of income.

In table 4, 21 per cent (73) of members of departments of physiology in 1940 are listed as without doctorates. Twenty six of these had been lost in 1945, 15 to the armed forces and 11 by transfer to other fields. Of the 47 who remained, 40 had earned doctorates in the interval, 38 with promotions in

TABLE 7

Median professional incomes, and median number of years of professional service, in relation to academic ranks in departments of physiology, 1940 and 1945

	ANNUAL PROFESSIONAL INCOME MEDIAN, \$		YEARS SINCE ENTRY INTO PROFESSION MEDIAN	
	1940	1945	1940	1945
Department heads	5900	6200	19	21
Professors	4900	5100	20	20
Associate professors	4050	4250	12	13
Assistant professors	3100	3650	8	6
Associates and instructors	2150	3000	2	4

group had some increase of earnings between 1940 and 1945. This was brought about mainly by promotions and transfers. In non-commercial institutions for research and teaching, where the majority of physiologists are employed in peacetime, basic salary scales apparently were raised somewhat in the lower ranks, but very little if at

all in the higher. In the lowest ranks the increase of income was perhaps sufficient to offset the increase of taxes and of general price levels. But the economic status of the average department head,

TABLE 8

Personnel with doctorate degrees in departments of physiology, 1940 and 1945. Transfers to and from other fields, changes in rank, and new appointments

Total number in departments of physiology, 1940	273
Lost between 1940 and 1945	
Transferred to other departments	20
Transferred to non academic civilian positions	12
In armed forces, 1945	24
Retired between 1940 and 1945	5
Unemployed, 1945	2
Held over through 1945	
At same rank as in 1940	98
At lower rank	4
Promoted in rank	99
Added between 1940 and 1945	
With doctorates conferred 1940-1944	76
With doctorates dated 1939 or earlier	
Transferred from other departments	24
Transferred from non academic positions	9
Total number in departments of physiology, 1945	310

professor, or associate professor in physiology had obviously deteriorated in 1945, as compared to the status of corresponding ranks in 1940. In war time many people, of whom physiologists make up only a small fraction, inevitably find themselves in a similar situation. We are actually not concerned now about 1945, but about the future. If the cur-

rent trends toward general higher pay and price levels continue, and if salaries in physiology remain static, it seems clear that increasing economic difficulties will face those now working in the science, and that fewer young men will choose to enter it.

If physiology is to attract capable men, as it must do if its progress is to continue, there must be available a sufficient number of more or less permanent positions, in research and teaching, at salaries commensurate with those offered in competing fields. Plans are now being developed for the advancement of scientific research through governmental support. These plans make impressive provision for the training of young men in the sciences, but are regrettably vague with respect to the subsequent employment of the men trained. Section IV of this report will show that many men already trained in physiology have left it because it had too little to offer in the way of a career.

No doubt a certain amount of shifting between physiology and related fields is wholesome. Nor is it necessary, or even desirable, that every man who enters physiology with a doctor's degree should automatically be advanced in a few years to a professorship or the equivalent. There should be competition for the higher positions. But in any long-range program, an attempt should be made to reach a proper balance between the number of men trained and the degree of advancement which the majority of them can reasonably expect to achieve. For the formulation of such a program factual information is required, it is hoped that the material here presented may be of use.

SECTION IV THE CAREERS AND INCENTIVES OF PHYSIOLOGISTS

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The careers, ambitions, concepts and incentives of physiologists cannot be subjected to precise tabulation and statistical analysis as have been their geographic distribution and economic status. Wherever possible in this report the opinions expressed by physiologists have been treated numerically. The remainder represents an attempt at a synthesis of the comments made by physiologists in answer to our request for criticism of present teaching methods and for "expression of opinion on any matters dealing with the advancement of physiology" (including publication facilities, meetings, employment services, new fields of employment and obligations of physiologists to society). The comments that follow are included either because they were offered by a number of

individuals or because they are considered to be thought provoking. The committee does not necessarily agree with all of these comments but feels that they are well worth recording here.

The careers of physiologists are concerned chiefly with research, teaching, and the training of young men and women.

A. Research. Three hundred physiologists who reported for themselves and associates had budgets totalling three million dollars in 1945 (exactly double that in 1940). The precise percentage of these budgets assigned to research is not known but at least 25 times as much was expended on research as on teaching. The continuity of this financial support is uncertain: only 8% of the group had "long term" grants exclusively and

66% of all the grants were classed as "short term" While department heads had the largest per capita budget, only 27% of the total funds in 1945 were administered by the department heads, 44% were administered by professors other than department directors and 29% by those below the rank of professor This may be a recent situation caused by government grants to individuals for wartime research

Conditions were considered reasonably satisfactory for research by 82% of the group Most medical schools encourage physiological research though many smaller colleges or universities do not The most serious difficulty encountered in research work was the lack of trained technical helpers and research assistants 75% of physiologists reported inadequate technical help This lack of assistants is related directly to size of budget Of those reporting annual budgets of \$100,000 or more, only 14% found their technical helpers inadequate Of those with budgets of \$25,000 to \$50,000, 54% claimed inadequate helpers and of those with budgets of \$5000 or less 85% were dissatisfied It is apparent that good technical helpers do not exist but that these are attracted to the research institutes where salary and permanency are not problems Other difficulties encountered in research were (in order) too much time required by teaching, too much time taken up by other duties and lack of physical equipment

B Teaching Only 10% of the group have no teaching responsibilities Most of the group teach medical, dental or graduate students and only 10% teach undergraduate students primarily The median medical school course in physiology consists of 99 lectures and 154 hours of laboratory work The spread is wide 55 to 228 lectures and 96 to 354 hours of laboratory work The minimum number of lectures and the maximum amount of laboratory work belong to Missouri, where the students must be *shown* and not told!

85% of physiologists believe that conditions are reasonably satisfactory for teaching Of the minority reporting serious handicaps, these are (in order) (1) classes too large for the staff, (2) lack of technical help, (3) too many hours of teaching required and (4) lack of physical equipment

Some specific constructive comments in regard to teaching were

(1) There is a need for more modern equipment in teaching X-ray, fluoroscope, electrocardiograph, electroencephalograph, cathode ray oscilloscope One individual reported aptly, "We need a moratorium on the inductorium"

(2) More visual teaching aids should be made available (such as moving pictures made or directed by authorities in special fields for distribu-

tion to colleges and universities where physical equipment is scarce)

(3) Exchange teaching professorships and instructorships should be fostered

(4) A handbook of physiological data, similar to the Handbook of Physics and Chemistry, should be published

(5) A comprehensive manual of physiological laboratory experiments should be assembled

(6) The teaching of physiology in medical schools should be expanded The most frequent comments upon teaching referred to the question of teaching physiology in the various years of the medical curriculum While a few believe firmly that medical physiology should be taught as a pure science, the great majority agree that the teaching of physiology should be correlated more closely with that of other medical sciences biochemistry, pathology pharmacology, medicine, and surgery Only 27 of 69 medical schools teach physiology in the second year in addition to the first, and only 15 of these present more total hours than the median One school lists the teaching of physiology in the third year and one in the fourth year It is becoming apparent to clinicians that physiology is now displacing morphology as the fundamental medical science Physiological teaching and orientation is now needed for medical students in all four years, for internes, for residents, for graduate physicians and for those aspiring to be licensed as medical specialists At present less than 8% of physiology teachers instruct in clinical physiology, though 36% have the M.D. degree The extension of the teaching of physiology into the third and fourth years of medical school can be accomplished by the creation of clinical physiology courses, seminars or ward walks It can probably be accomplished better by making physiologists of our future clinical teachers This will be considered in greater detail later

C Training of physiologists A third function of physiologists is considered to be the training of young men and women in physiological techniques and thinking Physiology has two great tasks in the future, (1) to spread physiology and physiological methods into all of medicine, tending to convert medical teaching from descriptive, morphological aspects to functional aspects, and (2) to delve into the mysteries of the cell and learn more of the fundamental processes of life The same man will only rarely acquire the training needed for those two undertakings Cellular physiologists require much more training in physics, chemistry and mathematics than premedical students obtain On the other hand the cellular physiologist rarely spends four years in acquiring the M.D. degree While the most spectacular and widely publicized activities of physiologists are

those concerned with human disease and its treatment, the growth of pure or of general physiology must be encouraged in every way. In a program for training new physiologists, equal emphasis should be placed upon the training of doctors of physiology and of doctors of medicine.

More physicians should become interested in physiology, not necessarily with the view of becoming full-time physiologists but to learn more of the experimental approach to clinical problems and teaching. This may be accomplished:

(1) By the insistence that classes in medical physiology be presented by those who teach, not grudgingly, but from the fascination of educating, inspiring and stimulating young men.

(2) By the interpretation to clinicians of fundamental advances in physiology by those physiologists who write or speak lucidly and concisely.

(3) By the establishment of research student-ships in physiology—if only during the summer months.

(4) By encouraging admission to medical schools of students who are interested fundamentally in research or teaching—not in practicing medicine.

(5) By the establishment of one year or several-year fellowships in physiology as part of the medical and surgical resident and specialist training programs.

(6) By freeing the most inspiring and stimulating physiologists from administrative work so that they may devote considerable time to the training of these men.

Since general or cellular physiologists usually do not come from the ranks of physicians, an entirely different program must be initiated to attract more men into this field. The prospective Ph.D. in physiology, if not an M.D. as well, must receive his initial enthusiasm for physiology in college. At present most college courses in biology are concerned primarily with anatomy and morphology and less with function. Non-premedical students should be exposed to the stimulation of a good experimental biology course in college. Colleges might be prodded into the development of such courses by the medical schools. At present no medical school in the country requires any pre-medical instruction in general physiology. Only two advise physiology as a premedical subject, three indicate that it *may* be taken, 49 make no mention of physiology, general physiology or comparative physiology. On the other hand 17 medical schools request, urge or recommend that college courses in physiology *not* be taken, or if taken, will not help satisfy medical school requirements. While it is realized that the whole subject of premedical requirements is a highly controversial matter, it has been suggested that if medical schools recommend that general physiology be taken in college, this might be sufficient to pro-

mote the extension of physiology in some 400 colleges throughout the country.

It is unsound to attempt to increase the number of physiologists in the country only to find that no teaching or research positions are available for them. This can be remedied only by making available funds for the support of general physiology not only in medical schools but in colleges as well.

At present, salary scales are so low in some colleges and medical schools that many men and women who desire to do research or teaching in physiology are forced into other fields through the sheer necessity of supporting their families. A supplementary questionnaire was sent to all directors of physiology departments requesting that data be supplied in regard to all their staff members and graduate students during the ten-year period 1935-1945. Fairly complete information was returned by 35 medical school departments, 2 college departments and 2 graduate research institutes. Data upon 527 individuals were analyzed. Of these 527, 313 are still working full or part time in medical school, college or governmental physiology departments or in the related preclinical fields of biochemistry or pharmacology. The other 214 have left physiology for various reasons. 130 are practicing medicine, 25 are in the armed forces, 18 (women) are married, 14 have entered business careers, 12 are in commercial laboratories and 15 left for miscellaneous reasons. Of this group of 214, 61 had received Ph.D. degrees in physiology and 60 had received M.A. or M.S. degrees in physiology. Students who have temporarily entered physiology as a deliberate preparation for clinical medicine have not been included knowingly in these figures. Consequently it appears that a very high percentage of those who desire a career in physiology leave this field. It is impossible to ascertain how many of these might have become outstanding teachers or investigators. However it is certain that many individuals either leave or do not enter upon an academic career because of the discouraging financial outlook. Some directors of physiology departments have tried individually to remedy this situation by refusing to make appointments at substandard salary scales.

There is evidence that physiologists are not motivated strongly by desire for riches. Physiologists are rather conservative in their estimates of what constitutes "fair and adequate salaries." Directors of all medical and many college physiology departments were requested (in a supplementary questionnaire) to answer the following question: "What salaries do you consider to be fair and adequate at the present time (April 1946) for physiologists?" So few replies were received from the colleges that only data will be considered from the 46 medical schools that answered. Table

1 shows the actual annual salaries received by physiologists (in medical schools) in 1940 and 1945 and the opinions of the department heads regarding "fair and adequate" salaries. The medians of the salaries requested are Instructor \$3000, Assistant Professor \$4500, Associate Professor \$5600, Professor \$7500 and Department Head \$10,000. Even the highest incomes are extremely low compared with those of other medical specialists who have likewise risen to the top of their profession. Indeed, one frequently overlooks the point that physiologists, in common with pharmacologists, pathologists and biochemists are medi-

cists have commented frequently, in answering the questionnaire, that if they cannot be paid adequately in money at present they desire full payment by department heads and deans in their other incentives—freedom of investigation, freedom in teaching and in administration.

In addition to what has been summarized above, many physiologists have urged a few additional considerations:

(1) Representation of all physiologists in the American Physiological Society

(2) Further extension of new fields for physiologists—into colleges (including agricultural col-

TABLE 1

Actual annual professional incomes received by medical school physiologists as compared with salary scale considered "fair and adequate in April 1946" by 46 departmental directors

The median in each group is indicated by *

INCOME BRACKET	DEPARTMENT HEAD			PROFESSOR			ASSOCIATE PROF			ASSISTANT PROF			INSTRUCTOR		
	1940	1945	F & A 1946	1940	1945	F & A 1946	1940	1945	F & A 1946	1940	1945	F & A 1946	1940	1945	F & A 1946
\$10000 or over	3	6	22			5			1						
9000-9999	1	2			1	1									
8000-8999	2	4	11	1	1	12			1						
7000-7999	5	8	5	2	4	9*			6		1				
6400-6999	2	5	3	4	1	3			3			1			
5800-6399	9*	11*	2	1	3	8			10			4			
5200-5799	1	8				2	1	2	5*		2	2			
4800-5199	7	4		2*	8*	3	4	7	12	1	1	10		1	1
4400-4799	2	2		5	7	1	5	5	3			3	6*	1	
4000-4399	2	1		2	1		6	14*	3	7	10	15	1	2	2
3600-3999		1					7*	8	1	6	11*			5	
3200-3599	1	1		1	1		8	1		8*	16	6	4	4	7
2800-3199	2						5			5	7	1	1	9*	26*
2450-2799										2			6	2	
2350-2549										3	1		9	3	8
2150-2349													3*		
1950-2149										1			3	2	
1750-1949		1											6	2	
1550-1749	1												1	1	
Below 1550													10		1
No answer			3			2			1			1			0

Note: The data in columns headed 1940 and 1945 were obtained from 163 and 205 answers respectively to the original questionnaire; the figures in the column headed F & A 1946 were obtained from a supplementary questionnaire answered by 46 department directors.

cal specialists just as much as are internists, surgeons, obstetricians, or ophthalmologists, and that physiology as a medical specialty requires equal mental processes and equal or greater training than that demanded by clinical medical specialties.

Though many physiologists have changed professions for financial reasons, those who remain are motivated by a number of incentives. These are (1) the intense desire to perform original, independent investigative work, (2) the intellectual stimulus from colleagues, (3) the challenge in teaching students and in developing one's own teaching techniques and (4) security or tenure, retirement provisions and vacations. Physiolo-

gists, industry, drug companies, clinical research, aviation, clinical laboratories, governmental research, public health, entomology, etc.

(3) A further development of the Federation Employment Bureau with public listing of available positions in Federation Proceedings by those desiring to do so—to replace the grapevine system of job location.

(4) A public relations bureau to provide the press and general public with accurate, interesting accounts of research in Physiology in order to supersede grossly inaccurate articles in national magazines which only serve to confuse the public. Such a bureau should also serve to educate the public as to the purpose, method and value of

basic physiological research and its need for public encouragement

A more detailed *Digest of Comments and Sugges*

tions has been written by Dr Philip Dow, and mimeographed copies are available upon request to him

SECTION V FUTURE PHYSIOLOGY

E F ADOLPH

The University of Rochester

Physiology today is an evolution from its own past. Its main theme is circulation largely because Harvey and others found ways of securing exact information about the blood's circulation. It is subdivided according to anatomical terms largely because processes were first studied from curiosity about structures. It is analytical in method largely because its devotees were teachers. Its investigations are reported in short papers largely because most of its students were part-time observers who had no connected time to write books. Research tends to be routine and outlook on reality is limited because no physiologist stops to analyse the basic assumptions of present science, and few suspect that other procedures than those of the past are available.

Let us say with Cousin, "It is better to have a future than a past." If so, it behooves us to gain a glimpse, or possibly a vision, of how much is yet to be done in physiology.

What of the Future? A historian who might be called upon to assess the position of the physiologist today would start from a consideration of social organization. He would speak of the development of civilization, the obligation of the individual to the society in which he lives, the allegiance of the professional man to his profession, the incentives that result in effective accomplishment, and the unique craving for freedom by the human spirit. By listing the notions and residues upon which our social world is based, the historian would lay foundations upon which specific and decisive formulations about intellectual position could emerge. In contrast, the scientist is likely to take for granted the social organization that has made scientific outlook and endeavor possible. All that distinguishes western civilization from any other would be absent in his description of backgrounds. Or would it be absent? Rather it would be implicit, yet apparent to the philosopher capable of visualizing all that the scientist of today, specialist and man of action, ignores in his description of life processes. Today's scientific outlook may not survive under some other trend of social organization.

A question before all scientists today is: Why not push onward within the frame provided by

existing customs and institutions? Why not stay in the laboratory where one has a small sphere of freedom, instead of upsetting much peace of mind in the effort to explore the wider implications of scientific endeavor? Society itself does not want to be disturbed by thinkers or experimenters. Shall one accept the niche in which accident and evolution have placed one, or explore other niches to see what their advantages and disadvantages may be? Such exploration calls for a different type of experimentation than the manipulation of apparatus. It calls for experimenting in social ideas, in concepts of what scientists can do, and most profitable of all, in rearranging one's own notions of what is worthwhile and of what can be done with the advances in knowledge as we reach them. Perhaps a larger purpose may in the end be formulated by each physiologist who starts to explore.

Estimate of Physiology's Task. Doubtless numerous physiologists have at some time wondered how many phenomena of life are still to be investigated. If it be possible to define one process (e.g., formation of carbonic acid), it may also be possible to estimate the hundred varieties of conditions (e.g., temperature) under which that process could be manifested. Unfortunately, living systems can but rarely be divided into unit processes. Nevertheless, let us suppose that some living cell has a thousand unit processes. Among the billions of cells in one organism the majority of processes are similar, another thousand might be added as variants. In the compounding of the cells into organs another thousand unit processes emerge, and perhaps another thousand in becoming a whole organism. Thus under one set of conditions there are 4000 unit processes to be studied in one individual. The interrelations among the processes are likely to be not 4000² but $\sqrt{4000}$, which is a superastronomical number. Perhaps in one species the peculiarities of the individual are only in one per cent of the unit processes, but among the billion individuals belonging to the species another million new units might be found. Further, among the several million species, millions of new processes and billions of new interrelations will be found, even though the majority of them will be uniform throughout thousands of species and their

parts. Such an estimate is quantitatively useless, but it visualizes the inexhaustible material that awaits physiological study. Certainly short cuts will be found by the explorers on the trail, and comprehensive procedures will save much labor. Nevertheless, for generations to come the factual frontier will remain endless.

If the factual content of physiology counts its units by millions, the intellectual content of physiology is also infinite. Compared to the hundred physical techniques now available, thousands can be developed. Mathematical and logical techniques alone may number more thousands. Devices for conceiving, visualizing, and reasoning about living processes and their interrelations may become myriad. The task of physiology is continually to invent new approaches. There is already reason to believe that more non-Harveian physiologies can exist than non-Euclidean geometries.

The Immediate Future. About the immediate future, much more concrete notions can be formulated. One comprehensive notion of the aims of physiology is that physiology like all science consists in arriving at generalizations. A list might be made of today's generalizations in physiology. A visible enemy to the testing of general rules is the specialization of knowledge. Therefore present compartments may to advantage not be maintained. Free lances may advantageously appear among physiologists. They may garner results from many sorts of physiology and weld them into more general categories of fact and concept. They will need at one time the concrete experience of the aged physiologist and the initiative of the young novice.

Some physiologists are concerned to predict the likely directions in which physiological research will develop in the next 25 or 50 years. It is not clear that the subject matter or topics of research will themselves be decisive. Nor do the new physical tools that will become available seem important, though they will steer men's attentions. Rather we may ask, what *kinds* of results and achievements will at that time be awarded most recognition?

One guess among the infinite number that can be made in this area, is the following. Physiologists will by induction achieve generalizations for many processes susceptible of physical analysis. Since we are in an age and place of instrumental skill, we will make available enormous numbers of measurements by the most ready methods. Knowledge of these processes will continue for many years to overshadow our concepts concerning processes not measurable by those same methods. Later will come the appreciation of the means by which the measured properties are interrelated and by which the interrelations have been estab-

lished (hatched) and by which they can be unhatched and rehatched. In that day measurements will be valued only as they ascertain the degree of modifiability in the life of the living system, perhaps. New processes will no longer be merely identified, but their evolutionary history and present lability will be assessed.

At the same time that induction is carried to increasing heights of generalization, deduction will occupy many physiologists. New applications will be found in proportion as uses in everyday life seem to demand them. Every industry will involve physiological applications, if for no other reason than that it has workers in it who are compounds of physiological phenomena. In addition, the majority of industries will probably make use of animals, microorganisms, and plants, and those industries need subjection of those organisms to the control and productivity that only physiology can furnish. Instead of limiting itself to diseases of man and reproductive products of hens and cows, physiological science will exploit thousands of organisms as fast as genetics produces profitable types. But physiologists will set the specifications required of those types.

Publications. The survey has included no information about publications by physiologists. We might count the total number of titles listed in some standard index, if physiology be defined in some arbitrary way. It could be demonstrated that the number of papers published has increased annually in some particular progression. The committee is inclined to the view that the numbers of publications have little to do with the advancement of physiology, but that the kinds of publications may be important.

Current research is largely conceived in terms of "papers" each ten pages in length. Somehow this type of report has evolved, it represents the median effort of physiologists. The point we wish to make is that the type of report now wags the type of research. Whether this fact is beneficial or not for the state of physiology is difficult to judge. Instead of judging, we can picture some possible alternatives.

A report states the results of what the investigator conceives to be a complete decision of some question or a comprehensive description of some process. Completeness, of course, varies with the individual and the topic. Often the author of the report feels urgency to make his results known, often not. Pressure to undertake some other study may lessen the completeness of the first one. Let us now imagine a scientific regime in which everyone planned his work five years ahead and was never deflected from his plans by economic and geographical influences. The result might be that much or most work would be reported in monograph form, for many temperaments would allow

ordering of the investigations so that they ultimately formed a connected whole. Such a result would make enormous differences in the types of investigation undertaken, the forms of thinking used, the methods of observation applied, and the insight of organisms attained. It would be an extreme regime of individualistic research.

Again let us suppose that political nationalism gripped the world to the point where no one wished his work known outside his own country. At the same time, transportation being quick and economical, all scientific results can be aired in group conferences. Film copies of data and abstracts may be distributed the same day that a conclusion has been reached. Then scientific reporting would be much like weather reporting. Either no permanent record of the efforts of individuals would be kept, or the individual's contributions would be lost in some collective synthesis that would be continuously made by specialists in synthesis. Thereupon the objectives in research would not involve individual credit but rapid socialized accumulation. The character of scientific work would inevitably shift to that which can be done cooperatively but with little continuity in the mind of the individual. Every aspect would have been explored in conference before the form of the synthesis had been published. The regime would be an extreme of socialistic research.

These two examples indicate two trends in present-day physiology. They show that publication is not merely a superficial manifestation of end results, a by-product of investigation, but is an integral part of all scientific effort. Even the purest amateur is influenced by the possibility of making a contribution, hence of putting his conclusions into permanent form.

It seems unlikely that the aims of science are served by merely burying results in a publication. What will be done with the yield from investigations is a question that reaches far beyond the initial stages of potential dissemination of printed words. Somewhere in the social organism may be found individuals who are not too preoccupied, to explore the connections of various fruits of research both with the theory of the universe and with the practices of society.

Another direction in which publications themselves are influential is in some of the relations of physiology with the public. All publication implies that results are for the use of whoever finds a value for them. But publication can also be a vehicle that represents to the wide public that for which it is paying. One respondent to the survey questionnaire remarked that "Physiologists are not capitalizing on the interest which laymen have in the human organism and in animals. Public opinion and public support of physiological science would be increased at least 200 per cent if good

popularization were carried on. Public school instruction should be a major part of a long term program."

Everyone knows that it is more difficult to write or speak for a popular audience than for a specialized. But the ultimate support for scientific research and for its freedom of action depends largely upon the trouble that scientists take to broadcast to everyone an understanding of their motives, their methods, and their needs as well as of their end results (Bernal, 1939). Organized efforts are undoubtedly needed in each field of science to emphasize, guide, and aid this effort. Our own confusion in a field of physiology that is unfamiliar to us is an inkling of how meaningless the whole of physiology can be to the layman. Evidently physiologists have much yet to do before they have delivered their product to the population of the world at large.

It is inevitable that in the future the forms of publication will influence both the nature of physiological research and the recognition of physiology in general. Therefore conscious efforts are continuously required to fit publications to the needs of scientists and of society.

Social factors. Questions of the utmost imaginative practicability are foreseen in the next 50 years. The most general one is: Will society be modified in such a way that it favors or discourages effort in physiology? And what factors will favor such effort? Intellectual factors will largely depend, it may be supposed, upon success in educating creativeness. The genetically endowed individuals will be found and encouraged. We now think that encouragement comes from contact with original and talented minds, from freedom of choice of activities, and from incentives both moral and economic.

Better than devising a new pattern for the future of physiology would seem to be the exercise of imaginative foresight in diverse situations as they arise. The privilege of planning for the future is one that continues, and hence must be kept from fixity. In an age when social security seems to many the greatest asset in any job, physiologists must plan for security. But when competition in exploring the theory of life, or in preventive medicine, or in environmental survival, seems most important to society, then physiologists must set their sights accordingly.

One guess is that physiology will in 50 years be only incidentally a handmaiden to medicine, to industry, and to agriculture. In large part it will be a science in its own right, a basis for a theory of society, a criterion of reasoning in everyday life. This view is not a phantasy, because the foundations of science will to all but a few top theorists still be subconscious and therefore hourly useful. Physiology is developing methods of dealing with

complexities that may serve many sciences. The mental training obtainable in physiology may at that time be no "better" than that in any other field of endeavor, but it will be none the less basic to man. Moreover, the attitude of investigation may be uppermost in society, though hardly numerically so, and that attitude may overshadow the facts and applications of physiology.

Within this 50 year period great social and political questions will influence physiology. Some specific questions will be decided either for or by physiologists. These are: Will a career in physiological research be socially rewarding? Will the individual choose his own career and his own daily activities? Will physiology be a science or a technology? Will physiology be supported chiefly by governmental means or by other organized units? Will science dominate or be subservient to the material facilities used by it? Will it be drudgery? Will it have satisfying spiritual values as well as economic values? Will it continue to turn back to society enough results to compete with the returns from other social investments? Evidently the vision of physiologists may advisedly keep ahead of the vision of all others who would like to decide some of these questions without consulting physiologists.

SUMMARY Every physiologist at some time asks himself how we come to be doing what we do. The answer from history is that our activities have evolved largely by accident. Today's recognition of physiology as a profession is a by-product of a particular political and economic system, which happened to furnish a golden opportunity for our science. Today it is no longer necessary that all outlooks be dictated by accident. Perhaps now we are limited chiefly by our dearth of concepts—concepts about life processes, about methods of

synthesis of facts, or about quantitative measurements. One task of scientists is to keep their concepts out of ruts, they always need alternative views, a variety of working hypotheses. More concepts multiply scientific endeavor, if for no other reason than their mere variety. In the past it has not proven very fruitful to have special individuals as visionaries, hence it seems likely that most investigators will have to entertain unorthodox hypotheses with increasing frequency and with greater conscious effort. What physiologists undertake they generally accomplish, their undertakings can well be still more venturesome, their ventures depend on more variety of concepts.

Physiology has had its successive frontiers. The first frontier was concerned to find out how living organisms do what they do. It lasted from prehistoric times and had its heyday in the seventeenth to nineteenth centuries. The second frontier was concerned to secure recognition for physiology as a science and as a profession. It began to demand recognition in the eighteenth century with Boerhaave and Haller, and secured its place in the medical sciences. The claim for recognition is still going on in the gradual spread of physiology outside of medicine. The third frontier is concerned to embody its materials into a systematic science. It accepts the existence of facts, methods, and subject matter, and asks: What shall we do with them? It says: So what? Is physiology a hodge-podge or an edifice? Are there principles and generalizations, or only facts with no further meaning? Just now we are in an age where the third frontier has all the challenge, it has the disappointments and allurements that met those other pioneers, our predecessors. There are more frontiers over the horizon, tomorrow we have new lands to explore, and new hopes.

GENERAL CONCLUSIONS

Some of the findings about physiology in North America may be summarized. Each invites thought and action on the part of all members of the profession and its friends.

(1) Physiology has already proven itself an independent science requiring specific methods of study and special concepts. It is in process of winning its independence outside of medicine, as botany once did. It has also demonstrated useful applications to several technical fields of endeavor.

(2) Physiology is represented by about a thousand individuals in North America. Most of this number devote only 40 per cent of their time to investigation. Probably less than half of those who by first choice identify themselves with this science belong to the American Physiological Society.

(3) The greatest expansion of physiology in North America occurred 15 to 20 years ago. Since then its rate of gain of entrants has diminished and during war II has decreased. The estimated deficit of entrants into the profession during the war years already amounts to at least 150 individuals.

(4) Physiologists have in the past decade entered their profession at the rate of about 40 per year. The posts that they are filling were designed in a period when those above 40 years of age were a small fraction of the whole profession. Today half of physiologists have attained that age.

(5) Talent in investigation has been drained away from physiology into other activities where utilization of that peculiar talent has not been fully exercised.

(6) Research in physiology tends to be stereo-

typed Factors in this situation are (a) the prevailing belief that philosophical views do not concern research, (b) the aim for quick results, (c) the consciousness of impending publication, (d) the believed need for approval of others who will not devote time sufficient to evaluating radical departures, and (e) the fact that administrative abilities are encouraged by our present economic system above intellectual ones

(7) Professional unity does not extend to *all* physiologists, since approximately only persons interested in the processes of vertebrate animals apply the term to themselves. Physiology has satisfactorily filled only one niche (medical physiology) of the possible niches available to it. Workers in physiology who have no doctor's degree do not yet count themselves as belonging to a group (compare with chemistry)

(8) The tendency to formation of research teams has diminished the freedom of thought and action of younger physiologists

(9) Physiology has not yet been successful in conveying to the public an understanding of its capacities and needs. Interpretation to the lay man of the methods and objectives of discovery is lacking

(10) Monies spent for physiological research in North America are estimated at about 3 million dollars per year. This amount is judged to be a small fraction of the amount that could yield merely a directly profitable return in the present economic world. Technical help and freedom from routines are the items most immediately lacking in research activities

(11) Correspondingly, only an infinitesimally small fraction of the reckoned possible aspects and processes of organisms have yet been studied

REPORTS SUBMITTED BY SECRETARIES OF THE CONSTITUENT SOCIETIES

AMERICAN SOCIETY FOR PHARMACOLOGY AND EXPERIMENTAL
THERAPEUTICS, INC*Minutes of the meeting of the Society*

1946

The first regular business meeting was held on Tuesday, March 12 at 7 30 p m in Convention Hall, Atlantic City, New Jersey. President E F Nelson presided.

Dr L M K Geiling read the resolution prepared on Dr Herbert O Calvery, and Dr Arnold Welch read the resolution prepared on Dr V L Henderson. Both were accepted.

The following council recommendations were presented:

1) That the per member assessment per year to support the office of the Federation Secretary-Treasurer and the Federation Proceedings be \$2 00.

It was moved to accept this recommendation, it was seconded and the motion was carried.

2) That retired members pay the Federation assessment of \$2 00 per year if they wish to receive the Federation Proceedings.

It was moved to accept this recommendation, it was seconded and the motion was carried.

3) That the exemption from payment of dues extended to members in the Armed Forces be discontinued as of this fiscal year.

It was moved to accept this recommendation, it was seconded and the motion was carried.

4) That the Society express its enthusiastic approval of the purposes of the Society for Medical Research and will recommend further action when the most effective means of assistance become evident, and that it also endorses most heartily the activities of the Friends of Medical Research.

It was voted to accept this recommendation, it was seconded and the motion was carried unanimously.

It was moved that the members be given an opportunity to make personal financial contributions (through the treasurer of our society) to the Society for Medical Research. This motion was seconded and then unanimously carried.

The president announced that the next meeting of the Federation would be held in Chicago, the week of May 18, 1947, at the Stevens and other hotels as the guests of the University of Illinois.

The Amendments to the Constitution and By-Laws were brought up and discussed.

It was moved, seconded and approved that the revision of Article III, Sec 1 and 2c be reworded

and submitted to a vote at the second business meeting.

The revision of By-law 1 as moved, seconded and carried is as follows:

"Papers to be read shall be submitted by members of the Society to the Secretary who, with the President shall be empowered to arrange the program. No person may orally present more than one paper. In case of joint authorship the name of the individual who will orally present the paper shall stand first. Papers not read shall appear on the program as read by title."

The treasurer read his report. Drs Roth and Van Winkle were appointed auditors.

The report of the Editor in Chief was read by the President. It was moved that the report be accepted, seconded and the motion was carried.

The election of officers was next held. The following officers were elected: President, M H Seevers; Vice-President, H B van Dyke; Treasurer, McKeen Cattell; Secretary, H B Haag; Membership Committee, C M Gruber; Council, Hamilton Anderson, J C Krantz; Nominating Committee, K K Chen, Chairman, Alfred Gilman, P F Knoefel, Carl Pfeiffer, Robert Woodbury.

It was moved, seconded and carried unanimously that the local committee be given a vote of thanks for the success of this, the first post-war meeting.

The meeting was adjourned at 9 30 p m.

The second regular business meeting of the Society was held on March 14, 1946, at 11 00 a m in Convention Hall. Dr E E Nelson presided.

The twenty-three proposals for membership listed in the report of the 3rd Council Session were elected to membership.

It was moved, seconded and approved that Dr Woodbury's suggestion that the change in Article III section I of the Constitution be dropped.

The rewriting of Article III section 2C was submitted as follows:

"Candidates reported upon by the Membership Committee to the Council may be recommended for admission by the Council only provided they have been approved by four-fifths of the combined membership of the Membership Committee and the Council."

It was moved, seconded and approved that this change be adopted.

The auditors reported that the Treasurer's

accounts were in good order. It was moved to accept the report of the Treasurer. The motion was seconded and unanimously carried.

It was moved that the dues for the conduct of the Society be continued at \$2.00 for the coming year, and that the dues for the Federation Assessment be \$2.00 (total \$4.00 per member per year). This motion was seconded and carried unanimously.

It was moved by Dr. Knoefel that a committee be appointed to consider further publications by the Society, such as a Review, a Handbook and a Toxicology. The motion was seconded, favorably discussed and carried.

The meeting was adjourned at 1 p.m.

ANNUAL MEETING

CHICAGO, ILLINOIS, MAY 18, 19, 20, 21 AND 22, 1947

The Federation will meet in Chicago, May 18, 19, 20, 21 and 22, 1947. Scientific and business meetings will be held Monday, Tuesday, Wednesday and Thursday. Sunday will be devoted to Council and Executive Committee meetings and to registration. In order to obtain hotel accommodations it was necessary for the Local Committee to guarantee occupancy of the hotel rooms on Sunday night. Since the scientific sessions begin promptly at 9:00 a.m. Monday, early registration on Sunday is desirable.

All of the functions will be centralized in the Stevens and Congress Hotels. This includes Federation headquarters, registration, Joint session, section meetings, symposia, motion picture demonstrations and smokers. Facilities for static demonstrations will be available at the University of Illinois on Tuesday afternoon and evening, the 20th. Programs and additional announcements will appear in the March issue of Federation Proceedings.

Registration will open at 9 a.m. on Sunday, May 18, at the Stevens Hotel. Members of any of the constituent societies and interested physicians, students or workers in biological laboratories may register. A registration fee of \$3.00 will be required. Admittance to the scientific sessions will be restricted to those who have registered. Programs, reprints, and tickets to the smoker and special functions will be on sale at the registration counter.

Hotel Reservations are to be made by means of letters to the hotels as soon as possible. The Local Committee has been promised the full cooperation of the Chicago Convention Bureau in securing the largest possible number of reasonably-priced rooms.

Deadline for Abstracts All abstracts of scientific papers and motion picture films must be received by the Secretaries of the individual Societies on or before February 14, 1947. "Regulations for the Preparation of Abstracts" and instructions for ordering reprints are given on pages 540-541.

Motion Pictures cannot be shown in the regular scientific sessions. However, a special section of the program will be organized for this purpose. Arrangements for presenting a film should be made by submitting to the Secretaries of the individual Societies the title and abstract of the film in the same manner as for a paper. In addition, the size of the reel and the length in minutes of the motion picture must be given. The time and place for the presentation will appear in the regular program. It will be necessary that someone familiar with the film be present at its showing. Sixteen millimeter safety film only can be shown and equipment for sound projection will be available.

An Informal Smoker is planned for Wednesday evening, May 21.

Local Committee The meeting is sponsored by the University of Illinois in collaboration with the other universities and research and teaching institutions of the Chicago area. The Local Committee includes Dr. G. E. Wakerlin, Chairman, and Dr. C. C. Pfeiffer, Secretary-Treasurer, and functions with the following sub-committee chairmen: Registration—Dr. C. I. Reed, Public Information—Dr. R. W. Gerard, Hotel Accommodations—Dr. F. J. Mullin, Program and Scientific Meetings—Dr. E. A. Evans, Motion Picture Exhibits—Dr. W. Van Winkle, Jr., Static Demonstrations—Dr. H. C. Wiggers, Projection Service—Dr. R. C. Ingraham, Communication Service—Dr. Julius Sendroy, Jr., Entertainment—Dr. L. N. Katz, and Women's—Mrs. C. I. Reed. The committee and its officers solicit any pertinent suggestions which might aid them in their duties.

Communications relative to the static demonstrations or other arrangements for the scientific meetings should be addressed to Dr. C. C. Pfeiffer, University of Illinois College of Medicine, 1853 West Polk Street, Chicago 12, Illinois. Inquiries about special luncheons and dinners and other similar functions should be sent directly to Dr. L. N. Katz, Michael Reese Hospital, 2900 Ellis Avenue, Chicago 16.

In order to facilitate registration, those attending the meeting may register in advance by mail up to and including May 15. Advance registrants should send registration fee and information (name, Chicago address, if known, home address, institution, whether full member, associate member or non-member, and constituent society of

membership or interest) to Dr C I Reed, University of Illinois College of Medicine, 1853 W Polk St, Chicago 12 The official badge may be claimed at a separate desk at registration headquarters

The members of the Federation in the Chicago area cordially invite their visiting colleagues to arrange to visit them and the institutions with which they are associated while attending the meetings The University of Illinois and the West Side Medical Center may be visited on Tuesday afternoon and evening during the time allotted to the static demonstrations

DONALD RUSSELL HOOKER

1876-1946

Dr Hooker's "classmates" as to age and time in our Physiological Society and our Federation, need not be told that in Dr Hooker's passing we have suffered a very great loss We agree, almost unanimously, that Dr Russell Hooker was one of the ablest and most devoted servants of our science This review and evaluation is directed to the younger workers in our ranks It may be worth their while to pause and ponder over the record of Dr D R Hooker

Born in New Haven, and receiving his preliminary education at Yale (A B, M S) and at Johns Hopkins (M D), Dr Hooker became a member (Assistant-Associate Professor) of the Department of Physiology at Johns Hopkins Medical School from 1906 till 1921 Dr Hooker thus became intimately associated with one of the great leaders in American Physiology of the past generation, Dr W H Howell Dr Hooker's personal investigations and publications during these years (circulation, respiration) point to Dr Howell's influence and guidance

When the American Journal of Physiology was turned over to the American Physiological Society in 1914 by its founder and editor, Dr W T Porter, Dr Hooker was appointed Managing Editor of this Journal, without salary, by the Council of the Society, and Dr Hooker served as the Managing Editor of our Journal for the subsequent 32 years For most of these years he served without salary or financial remuneration from our Society or from the Journal Until the establishment of our Society of the Board of Publication Trustees in 1933, Dr Hooker and his Editorial Board for the Journal worked under the direction of and reported directly to the Council of our Society I think it is fair to say (partly from personal experience) that both the Council and the Board of Publication Trustees were, in matters concerning the Journal,

largely guided by Dr Hooker's experience and recommendations

Now, what are the outstanding points in Dr Hooker's services to the American Journal of Physiology? Thanks to the founder and original editor, Dr W T Porter, the Journal came to our Society in 1911 (with Volume 34), with excellent heredity and character It was at that time almost self supporting, all the editorial work being done without financial remuneration Under Dr Hooker the Journal became not only self supporting, but *the source of a significant publication reserve fund for the Society* This fortunate development was due largely to Dr Hooker's perspicacity and persistent devotion Even through the late depression our publication reserve fund did not suffer the loss of a single penny

The *quality* of scientific publications is, of course, the first responsibility of the investigator reporting them But as Managing Editor, Dr Hooker insisted on accuracy, clearness, and brevity He tried to be, he was, fair and just to contributors He believed in, and he practiced the democratic way of life as editor In my experience, he never tried to sidestep the judgment of the majority of the Editorial Board as to individual authors and manuscripts He was not a dictator, he was a *leader* through his intelligence, his industry and his devotion to our science

In 1919 the American Physiological Society started the *Physiological Reviews*, an annual publication, largely on the wise plan and broad scope worked out by Dr Hooker Dr Hooker was appointed Managing Editor, aided by an Editorial Board, and he served in that capacity (for most of the years without salary) until his death this year The scientific, educational and financial record of the *Physiological Reviews* to date we owe in a large measure to Dr Hooker He displayed the same mental capacity and character here as he had abundantly proven as Managing Editor of the Journal Again, his Editorial Board appointed by the Council and by the Publication Trustees, was not a "window dressing" Somehow Dr Hooker managed (perhaps largely through his own example) to secure significant services from most members of his editorial boards

As the Secretary of the Physiological Society, I became in a way the first secretary of the Federation of American Societies for Experimental Biology for its first meeting in 1912 As regards the Federation, 1912 was the year of small beginnings In 1935 our Federation had reached such a size that a permanent secretary was clearly needed Dr Hooker was selected for that post and served as the efficient secretary and the editor of

our Proceedings till a few months before his death

This is a brief outline of Dr. Hooker's services to our science. Dr. Hooker, as I knew him, was the last man to claim the stature of a superman. I have not said that he never made a mistake, that even in his earlier years his judgment was entirely immune to personal preferences. But I have checked my own evaluation of the services of our departed colleague with many senior members of wide experience and known for objective impartiality. One of these men writes me: "I knew Dr. Hooker intimately the last fifteen years. A finer character I have never met. Being an editor was his way of serving science. His fine devotion was part of his own nature." In 1937 Dr. C. W. Greene wrote: "It has required long years of meticulous and patient work to plan and perfect the coordinations between the editorial boards, The Managing Editor and the Council necessary to establish our high publication standards. Throughout these years Dr. Hooker has given his scientific and editorial judgment as a labor of love for the cause of physiology" (*History of Am Physiol Soc*, 1938, p. 99). One colleague writes: "There have been criticisms of the Journals policies but when the critics investigated they came away to praise. They found that no one was more considerate of the author's rights than Dr. Hooker himself."

Very early in our association in the Physiological Society's work I perceived that Dr. Hooker's social conscience leavened his thinking and plans. If a man's social responsibilities parallel his understanding of man and nature, that responsibility on the part of a biologist is very, very great. Dr. D. R. Hooker tried to measure up to it.

The fact that the days of "blood, and sweat and tears" in the history of our Journal of Physiology had been weathered by Dr. W. T. Porter* when Dr. Hooker took the helm in 1914 does not lessen Dr. Hooker's services to our science. Our Society and our Federation are extremely fortunate in having had, from their beginning, such leaders in our scientific publication projects, men with the ability, the vision, the industry, and the unselfish devotion to our science, two such colleagues as Dr. W. T. Porter and Dr. D. R. Hooker. These two men, on their record, deserve from us a monument, the *living monument* suggested by a great teacher of the distant past (Luke, X, 37): "Go, and do thou likewise."

A. J. CARLSON

* See W. H. Howell, *History of the American Physiological Society*, pp. 78-83

EXECUTIVE COMMITTEE, 1947

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STANDING COMMITTEES

Defense of Biological Research A. C. LAY, *Chairman*, K. F. MYER, EPHRAIM SHORR
International Congresses D. W. BROOK, *Physiology, Chairman*, A. J. CARLSON, *Physiology*, D. D. VAN SLYKE, *Biochemistry*, E. K. MARSHALL, JR., *Pharmacology*, PRYTON ROUS, *Pathology*, L. A. MANNARD, *Nutrition*, J. J. BROUHAFFER, *Immunology*
Placement Service H. B. LEWIS, *Director*
Representatives, Council A. I. A. S. G. PHILIP GRABFIELD, C. GLIN KING
Federation Proceedings, Control Committee PHILIP BARD, *Chairman*, *Physiology*, C. G. KING, *Biochemistry*, C. F. SCHMIDT, *Pharmacology*, MORTON McCUTCHEON, *Pathology*, A. H. SMITH, *Nutrition*, A. P. LOCKE, *Immunology*

FORMER EXECUTIVE COMMITTEES

Philadelphia, Dec 28-31, 1913

S. J. MELTZER, *Chairman*, and A. J. CARLSON, *Secretary*, The Physiological Society. A. B. MACALLUM and P. A. SHAFFER, The Biochemical Society. T. SOLLMANN and J. AUER, The Pharmacological Society.

St. Louis, Dec 27-30, 1914

G. LUSK, *Chairman*, and P. A. SHAFFER, *Secretary*, The Biochemical Society. T. SOLLMANN and J. AUER, The Pharmacological Society. R. M. PEARCE and G. H. WHIPPLE, The Pathological Society. W. B. CANNON and A. J. CARLSON, The Physiological Society.

Boston, Dec 26-29, 1915

TORALD SOLLMANN, *Chairman*, and JOHN AUER, *Secretary*, The Pharmacological Society. THEO-

RAUL SMITH and PRYTON ROUS, The Pathological Society W B CANNON and C W GREENE, The Physiological Society WALTER JONES and P A SHAFFER, The Biochemical Society

New York, Dec 27-30, 1916

SIMON FINKLER, *Chairman*, and PRYTON ROUS, *Secretary*, The Pathological Society W B CANNON and C W GREENE, The Physiological Society WALTER JONES and STANLEY R BENEDICT, The Biochemical Society REID HUNT and J ALER, The Pharmacological Society

Minneapolis-Rochester, Dec 27-29, 1917

FREDERIC S LEE, *Chairman*, and CHARLES W GREENE, *Secretary*, The Physiological Society CARL L ALSBERG and STANLEY R BENEDICT, The Biochemical Society REID HUNT and L G ROWATRE, The Pharmacological Society LUDWIG HEATON and HOWARD T KARSNER, The Pathological Society

Baltimore, April 24-26, 1918

CARL L ALSBERG, *Chairman*, and STANLEY R BENEDICT, *Secretary*, The Biochemical Society REID HUNT and E D BROWN, The Pharmacological Society H GIDEON WELLS and HOWARD T KARSNER, The Pathological Society FREDERIC S LEE and CHARLES W GREENE, The Physiological Society

Cincinnati, Dec 29-31, 1919

A S LOEVENHART, *Chairman* and E D BROWN, *Secretary*, The Pharmacological Society W G MACCALLUM and HOWARD T KARSNER, The Pathological Society WARREN P LOMBARD and CHARLES W GREENE, The Physiological Society STANLEY R BENEDICT and VICTOR C MYERS, The Biochemical Society

Chicago, Dec 28-30, 1920

WILLIAM H PARK, *Chairman*, and HOWARD T KARSNER, *Secretary*, The Pathological Society WARREN P LOMBARD and CHARLES W GREENE, The Physiological Society STANLEY R BENEDICT and VICTOR C MYERS, The Biochemical Society A S LOEVENHART and EDGAR D BROWN, The Pharmacological Society

New Haven, Dec 28-30, 1921

J J R MACLEOD, *Chairman*, and CHARLES W GREENE, *Secretary*, The Physiological Society D D VAN SLIKE and VICTOR C MYERS, The

Biochemical Society C W EDMUNDS and EDGAR D BROWN, The Pharmacological Society F G NOVY and WADE H BROWN, The Pathological Society

Toronto, Dec 27-29, 1922

D D VAN SLIKE, *Chairman*, and VICTOR C MYERS, *Secretary*, The Biochemical Society C W EDMUNDS and EDGAR D BROWN, The Pharmacological Society HOWARD T KARSNER and WADE H BROWN, The Pathological Society J J R MACLEOD and CHARLES W GREENE, The Physiological Society

St Louis, Dec 27-29, 1923

C W EDMUNDS, *Chairman*, and EDGAR D BROWN, *Secretary*, The Pharmacological Society E L ORIE and WADE H BROWN, The Pathological Society A J CARLSON and CHARLES W GREENE, The Physiological Society PHILIP A SHAFFER and VICTOR C MYERS, The Biochemical Society

Washington, Dec 29-31, 1924

ALFRED S WARTHIN, *Chairman*, and E B KRUMBHAAR, *Secretary*, The Pathological Society A J CARLSON and WALTER J MEEK, The Physiological Society P A SHAFFER and D WRIGHT WILSON, The Biochemical Society JOHN AUER and E D BROWN, The Pharmacological Society

Cleveland, Dec 28-30, 1925

A J CARLSON, *Chairman*, and WALTER J MEEK, *Secretary*, The Physiological Society H C SHERMAN and D WRIGHT WILSON, The Biochemical Society JOHN AUER and E D BROWN, The Pharmacological Society GEORGE H WHIPPLE and E B KRUMBHAAR, The Pathological Society

Rochester, N Y, April 14-16, 1927

E C KENDALL, *Chairman*, and F C KOCH, *Secretary*, The Biochemical Society JOHN AUER and E D BROWN, The Pharmacological Society W H BROWN and E B KRUMBHAAR, The Pathological Society J ERLANGER and W J MEEK, The Physiological Society

Ann Arbor, April 12-14, 1928

CARL VOEGTLIN, *Chairman*, and E D BROWN, *Secretary*, The Pharmacological Society DAVID MARINE and CARL V WELLER, The Pathological Society JOSEPH ERLANGER and WALTER J MEEK, The Physiological Society E V MCCOLLUM and D WRIGHT WILSON, The Biochemical Society

Boston, Aug 19-24, 1929 **E**

(The XIIIth International
Physiological Congress)

EDWARD B. KRUMBHAR, *Chairman*, and CARL V. WELLER, *Secretary*, The Pathological Society. JOSEPH ERLANGER and WAITER J. MEER, The Physiological Society. E. V. MCCOLLUM and D. WRIGHT WILSON, The Biochemical Society. CARL VOEGTLIN and E. D. BROWN, The Pharmacological Society.

Chicago, March 26-29, 1930

WALTER J. MEER, *Chairman*, and ARTHUR C. REDFIELD, *Secretary*, The Physiological Society. W. R. BLOOR, and HOWARD B. LEWIS, The Biochemical Society. CARL VOEGTLIN and E. D. BROWN, The Pharmacological Society. WILLIAM F. PETERSEN and CARL V. WELLER, The Pathological Society.

Montreal, April 8-11, 1931

W. R. BLOOR, *Chairman*, and H. B. LEWIS, *Secretary*, The Biochemical Society. GEORGE B. WALLACE and E. D. BROWN, The Pharmacological Society. FREDERICK L. GATES and C. PHILLIP MILLER, The Pathological Society. WALTER J. MEER and ARNO B. LUCKHARDT, The Physiological Society.

Philadelphia, April 27-30, 1932

GEORGE B. WALLACE, *Chairman*, and V. E. HENDERSON, *Secretary*, The Pharmacological Society. SAMUEL R. HAYTHORN and C. PHILLIP MILLER, The Pathological Society. WALTER J. MEER and ARNO B. LUCKHARDT, The Physiological Society. H. C. BRADLEY and HOWARD B. LEWIS, The Biochemical Society.

Cincinnati, April 10-12, 1933

PEYTON ROUS, *Chairman*, and C. PHILLIP MILLER, *Secretary*, The Pathological Society. ARNO B. LUCKHARDT and FRANK C. MANN, The Physiological Society. H. C. BRADLEY and HOWARD B. LEWIS, The Biochemical Society. WM. DEB. MACNIDER and V. E. HENDERSON, The Pharmacological Society.

New York, March 28-31, 1934

ARNO B. LUCKHARDT, *Chairman*, FRANK C. MANN, *Secretary*, and ALEXANDER FORBES, *Treasurer*, The Physiological Society. W. M. CLARK and H. A. MATTILL, The Biochemical Society. W. DEB. MACNIDER and V. E. HENDERSON, The Pharmacological Society. CARL V. WELLER and C. PHILLIP MILLER, The Pathological Society.

Detroit, April 10-13, 1935

W. M. CLARK, *Chairman*, H. A. MATTILL, *Secretary*, and C. H. FISK, *Treasurer*, the Biochemical Society. CHARLES W. GREEN and FRANK C. MANN, The Physiological Society. R. A. HATCHER and E. M. K. GEILING, The Pharmacological Society. S. BURT WEINACH and SHIELDS WARREN, The Pathological Society.

Washington, March 25-28, 1936

V. E. HENDERSON, *Chairman*, E. M. K. GEILING, *Secretary*, and C. M. GRUBIN, *Treasurer*, The Pharmacological Society. FRANK C. MANN and ANDREW C. IVY, The Physiological Society. H. B. LEWIS and H. A. MATTILL, The Biochemical Society. OSKAR KLOTZ and SHIELDS WARREN, The Pathological Society.

Memphis, April 21-24, 1937

ALPHONSE R. DOCHFZ, *Chairman*, and SHIELDS WARREN, The Pathological Society. FRANK C. MANN and ANDREW C. IVY, The Physiological Society. HOWARD B. LEWIS and H. A. MATTILL, The Biochemical Society. V. E. HENDERSON and E. M. K. GEILING, The Pharmacological Society. D. R. HOOKER, *Secretary*.

Baltimore, March 30-April 2, 1938

WILLIAM T. PORTER, *Honorary President*; WALTER E. GARREY, *Chairman*, and ANDREW C. IVY, The Physiological Society. GLENN E. CULLEN and H. A. MATTILL, The Biochemical Society. ARTHUR L. TATUM and G. PHILIP GRABFIELD, The Pharmacological Society. C. PHILLIP MILLER and PAUL R. CANNON, The Pathological Society. D. R. HOOKER, *Secretary*.

Toronto, April 26-29, 1939

GLENN E. CULLEN, *Chairman*, and CHARLES G. KING, The Biochemical Society. ARTHUR L. TATUM and G. PHILIP GRABFIELD, The Pharmacological Society. C. PHILLIP MILLER and PAUL R. CANNON, The Pathological Society. WALTER E. GARREY and ANDREW C. IVY, The Physiological Society. D. R. HOOKER, *Secretary*.

New Orleans, March 13-16, 1940

E. M. K. GEILING, *Chairman*, and G. PHILIP GRABFIELD, The Pharmacological Society. ERNEST W. GOODPASTURE and PAUL R. CANNON, The Pathological Society. ANDREW C. IVY and PHILIP BARD, The Physiological Society. WILLIAM C. ROSE and CHARLES G. KING, The Biochemical Society. D. R. HOOKER, *Secretary*.

Chicago, April 15-19, 1941

SHIELDS WARREN, *Chairman*, and H. P. SMITH, The Pathological Society. THORNE M. CARPENTER and L. A. MAYNARD, The Institute of Nutrition.

ANDREW C ILL and PHILIP BARD, The Physiological Society WILLIAM C ROSE and CHARLES G KING, The Biochemical Society E M K GRILING and G PHILIP GRADFIELD, The Pharmacological Society D R HOOKER, *Secretary*

Boston, March 31, April 1, 2, 3, 4, 1912

ALBERT G HOGAN, *Chairman*, and ARTHUR H SMITH, The Institute of Nutrition PHILIP BARD and CARL J WIGGERS, The Physiological Society RUDOLPH J ANDERSON and ARNOLD K BALLS, The Biochemical Society E M K GRILING and R N BIETER, The Pharmacological Society JESSIE L BOLLMAN and H P SMITH, The Pathological Society SHIELDS WARREN, *Ex Chairman* D R HOOKER, *Secretary*

1943, 1944 1945 The meetings scheduled for Cleveland were cancelled because of war conditions

PHILIP BARD, *Chairman*, and WALLACE O'FENN,

The Physiological Society E A DOISI and ARNOLD K BALLS, The Biochemical Society E K MARSHALL, JR and RAYMOND N BIETER, The Pharmacological Society BALDWIN LUCKE and H P SMITH, The Pathological Society LEONARD A MAYNARD and ARTHUR H SMITH, The Institute of Nutrition JACQUES J BROUFEUBRENNER and ARTHUR F COCA, The Association of Immunologists D R HOOKER, *Secretary*

Atlantic City, Mar 11, 12, 13, 14, 15, 1946

PHILIP BARD, *Chairman*, WALLACE O'FENN, The Physiological Society A BAIRD HASTINGS and ARNOLD K BALLS, The Biochemical Society ERWIN E NILSON and RAYMOND N BIETER, The Pharmacological Society BALDWIN LUCKE and H P SMITH, The Pathological Society WILLIAM C ROSE and H E CARTER, The Institute of Nutrition JACQUES J BROUFEUBRENNER and ARTHUR F COCA, The Association of Immunologists D R HOOKER, *Secretary*

FEDERATION BY-LAWS

BY-LAWS

Adopted at the Washington Meeting, 1936 and amended at the Boston Meeting, 1942

1 The Presidents and Secretaries of the Constituent Societies, the Chairman of the Executive Committee of the preceding year and the Federation Secretary shall form the Executive Committee of the Federation

2 The Chairmanship of the Executive Committee shall be held in turn by the Presidents of the Constituent Societies, who shall succeed one another annually in the order of seniority of the Societies

3 The Executive Committee shall appoint annually from the membership of the Federation a secretary-treasurer, to be known as the Federation Secretary

4 The Federation Secretary shall (a) Keep the minutes of the Executive Committee and distribute copies to the Secretaries of the Constituent Societies (b) Make arrangements for the Annual Meeting with the Local Committee, with the approval of the Executive Committee (c) Print in convenient combined form and distribute to the membership of the Federation the programs of the Constituent Societies as received from their respective Secretaries (d) Undertake such other duties, to be decided upon from time to time by the Executive Committee, as do not conflict with the complete autonomy of the Constituent Societies

5 The Executive Committee shall control all monies in the hands of the Federation Secretary, who shall make an annual report to the Executive Committee for audit and approval The expenses of the Federation Secretary, as authorized by the Executive Committee, shall be the first charge on such monies and if insufficient for the purpose the Executive Committee shall prorate such expenses to the Constituent Societies of the Federation in proportion to their respective memberships

The Executive Committee may appropriate Federation monies annually for the uses of Local Committees and for the uses of other authorized Committees but in the latter cases an audit of expenditures shall be made and approved before such committees are discharged

6 The Executive Committee shall determine the place of the Annual Meeting, and the time shall be determined by the Local Committee, preferably within the period of March fifteenth to May first

7 The local Committee at the place of meeting of the Federation shall charge such fee for registration as may be approved by the Executive Committee The monies thus collected shall be used to defray the expenses of the Local Committee and the remainder, after such expenses have been met, shall be turned over to the Federation Secretary

8 The Executive Committee shall consider measures of advantage to the Federation as a whole Any Constituent Society may refer simi-

lar measures to the Executive Committee. No action, however, shall be taken by the Executive Committee unless specifically authorized by all the Constituent Societies.

9 The Chairman of the Executive Committee may appoint committees when the purposes of such committees have been approved by all the Constituent Societies of the Federation. Such committees shall be appointed for a term of one year, but may be continued and their members reappointed. Such committees shall report in writing to the Executive Committee, which shall in turn report thereon to the Constituent Societies either for information or recommendation. The Secretaries of the Constituent Societies shall report the recommendations of their respective Societies to the Executive Committee for final action.

10 All individuals whose names appear on the program by invitation or introduction and those registering from any recognized biological laboratory may be enrolled as Associate Members of the Federation for that Annual Meeting. Such Associate Members may enjoy all the privileges of the Annual Meeting except that of voting.

11 No person may present orally more than one paper during all of the scientific sessions of the Constituent Societies at the time of the Annual Meeting except upon invitation of the Executive Committee or a Council. Papers must be submitted to the Secretary of the Society of which the proposer is a member. The proposer may request transfer to another program, but this may only be done with the consent of the Secretary of the Society concerned. Any Secretary who regards any paper submitted to him as better suited to the program of another Society may arrange this transfer with the Secretary of the Society concerned, if it be possible. Such transfer shall be indicated on the program.

12 Abstracts not to exceed two hundred and fifty words in length, of papers approved for presentation at all of the scientific sessions of all the Constituent Societies at the Annual Meeting, shall receive publication in the *Federation Proceedings*.

13 A Control Committee, consisting of at least one representative of each Constituent Society as designated by the several Councils, shall have editorial control over the *Federation Proceedings* which shall be financed as required by an annual assessment of all the members of each Constituent Society.

14 The Control Committee shall have power to choose certain additional papers presented at the Annual Meetings and from other sources, including material heretofore published in the *Federation Yearbook*, for publication in the *Federation Proceedings*.

PLACEMENT SERVICE

The Federation maintains a service to act as a medium of communication between persons seeking positions for teaching or research and institutions that wish to fill vacancies in these sciences.

The service does not undertake to recommend or to pass judgment upon applicants. It aims merely to serve as a clearing-house for such information as above stated and to bring into touch with one another candidates for positions and vacancies to be filled.

Persons, whether members of the Federation or not, and institutions desiring to avail themselves of the service, may receive such information as is available without cost to the applicant.

All communications should be addressed to Dr. H. B. Lewis, Director, University of Michigan, Ann Arbor, Mich.

THE AMERICAN PHYSIOLOGICAL SOCIETY

Founded December 30, 1887, Incorporated June 2, 1923

OFFICERS ELECTED 1946

President—WALLACE O. FENN, University of Rochester, School of Medicine and Dentistry, Rochester, N. Y.

Secretary—MAURICE B. VISSCHER, University of Minnesota, Minneapolis.

Treasurer—D. B. DILL, Harvard University, Fatigue Laboratory, Boston, Mass.

Council—WALLACE O. FENN, MAURICE B. VISSCHER, D. B. DILL, CHARLES H. BEST, University of Toronto, Canada, HIRAM E. ESSEY,

Mayo Foundation, Rochester, Minn., W. F. HAMILTON, University of Georgia School of Medicine, Augusta, H. C. BAZETT, University of Pennsylvania School of Medicine, Philadelphia.

Board of Publication Trustees—ANDREW C. IVY, Chairman (1946-1949), HOMER W. SMITH (1944-1947), FRANK C. MANLY (1945-1948).

Representative on the Division of Biology and Agriculture of the National Research Council—FRANCIS O. SCHMITT (1945-48).

Representative on the Division of Medical Sciences

of the National Research Council—H C BAFTT (1914-47)

Representative on the Council of the American Association for the Advancement of Science—DAVID R RABORT with C J WIGGERS as alternate Historian—WALTER J MEEK

PAST OFFICERS

Organization Meeting, December 30, 1887

S WEIR MITCHELL, *President*

H N MARTIN, *Secretary*

1888 H P BOWDITCH, *President*, H N MARTIN, *Secretary-Treasurer*, J G CURTIS, H C WOOD, H SEWALL, *Councilors* 1889 S WEIR MITCHELL, *President*, H N MARTIN, *Secretary-Treasurer*, H P BOWDITCH, J G CURTIS, H C WOODS, *Councilors* 1890 S WEIR MITCHELL, *President*, H N MARTIN, *Secretary-Treasurer*, H P BOWDITCH, J G CURTIS, H H DONALDSON, *Councilors* 1891 H P BOWDITCH, *President*, H N MARTIN, *Secretary-Treasurer*, R H CHITTENDEN, J G CURTIS, H N DONALDSON, *Councilors* 1892 H P BOWDITCH, *President*, H N MARTIN, *Secretary-Treasurer*, R H CHITTENDEN, J G CURTIS, W H HOWELL, *Councilors* 1893 H P BOWDITCH, *President*, W P LOMBARD, *Secretary-Treasurer*, R H CHITTENDEN, J G CURTIS, W H HOWELL, *Councilors* 1894 H P BOWDITCH, *President*, W P LOMBARD, *Secretary-Treasurer*, R H CHITTENDEN, W H HOWELL, J W WARREN, *Councilors* 1895 H P BOWDITCH, *President*, F S LEE, *Secretary-Treasurer*, R H CHITTENDEN, W H HOWELL, W P LOMBARD, *Councilors* 1896 R H CHITTENDEN, *President*, F S LEE, *Secretary-Treasurer*, H P BOWDITCH, W H HOWELL, J W WARREN, *Councilors* 1897 R H CHITTENDEN, *President*, F S LEE, *Secretary-Treasurer*, H P BOWDITCH, W H HOWELL, W P LOMBARD, *Councilors* 1898 R H CHITTENDEN, *President*, F S LEE, *Secretary-Treasurer*, H P BOWDITCH, W H HOWELL, W P LOMBARD, *Councilors* 1899 R H CHITTENDEN, *President*, F S LEE, *Secretary-Treasurer*, W H HOWELL, W P LOMBARD, W T PORTER, *Councilors* 1900 R H CHITTENDEN, *President*, F S LEE, *Secretary-Treasurer*, W H HOWELL, W P LOMBARD, W T PORTER, *Councilors* 1901 R H CHITTENDEN, *President*, F S LEE, *Secretary-Treasurer*, W H HOWELL, W P LOMBARD, W T PORTER, *Councilors* 1902 R H CHITTENDEN, *President*, F S LEE, *Secretary-Treasurer*, W H HOWELL, W P LOMBARD, W T PORTER, *Councilors* 1903 R H CHITTENDEN, *President*, F S LEE, *Secretary-Treasurer*, W H HOWELL, W P LOMBARD, W T PORTER, *Councilors* 1904 R H CHITTENDEN, *President*, W T PORTER, *Secretary-Treasurer*, F S LEE, W P LOMBARD, W H HOWELL, *Councilors* 1905 W H HOWELL,

President, L B MENDEL, *Secretary*, W B CANNON, *Treasurer*, R H CHITTENDEN, S J MELTZER, *Councilors* 1906 W H HOWELL, *President*, L B MENDEL, *Secretary*, W B CANNON, *Treasurer*, A B MACALLUM, S J MELTZER, *Councilors* 1907 W H HOWELL, *President*, L B MENDEL, *Secretary*, W B CANNON, *Treasurer*, J J ABEL, G LUSK, *Councilors* 1908 W H HOWELL, *President*, R HUNT, *Secretary*, W B CANNON, *Treasurer*, J J ABEL, G LUSK, *Councilors* 1909 W H HOWELL, *President*, R HUNT, *Secretary*, W B CANNON, *Treasurer*, A J CARLSON, W P LOMBARD, *Councilors* 1910 W H HOWELL, *President*, A J CARLSON, *Secretary*, W B CANNON, *Treasurer*, J ERLANGER, F S LEE, *Councilors* 1911 S J MELTZER, *President*, A J CARLSON, *Secretary*, W B CANNON, *Treasurer*, J ERLANGER, F S LEE, *Councilors* 1912 S J MELTZER, *President*, A J CARLSON, *Secretary*, W B CANNON, *Treasurer*, J ERLANGER, F S LEE, *Councilors* 1913 S J MELTZER, *President*, A J CARLSON, *Secretary*, J ERLANGER, *Treasurer*, W B CANNON, F S LEE, *Councilors* 1914 W B CANNON, *President*, A J CARLSON, *Secretary*, J ERLANGER, *Treasurer*, F S LEE, S J MELTZER, *Councilors* 1915 W B CANNON, *President*, C W GREENE, *Secretary*, J ERLANGER, *Treasurer*, W E GARREY, W H HOWELL, J J R MACLEOD, W J MEEK, *Councilors* 1916 W B CANNON, *President*, C W GREENE, *Secretary*, J ERLANGER, *Treasurer*, W E GARREY, W H HOWELL, J J R MACLEOD, W J MEEK, *Councilors* 1917 F S LEE, *President*, C W GREENE, *Secretary*, J ERLANGER, *Treasurer*, W B CANNON, W H HOWELL, J J R MACLEOD, W J MEEK, *Councilors* 1919 W P LOMBARD, *President*, C W GREENE, *Secretary*, J ERLANGER, *Treasurer*, W B CANNON, Y HENDERSON, J J R MACLEOD, W J MEEK, *Councilors* 1920 W P LOMBARD, *President*, C W GREENE, *Secretary*, J ERLANGER, *Treasurer*, W B CANNON, J J R MACLEOD, Y HENDERSON, C J WIGGERS, *Councilors* 1921 J J R MACLEOD, *President*, C W GREENE, *Secretary*, J ERLANGER, *Treasurer*, J A E EYSTER, Y HENDERSON, C J WIGGERS, A J CARLSON, *Councilors* 1922 J J R MACLEOD, *President*, C W GREENE, *Secretary*, J ERLANGER, *Treasurer*, Y HENDERSON, C J WIGGERS, A J CARLSON, J A E EYSTER, *Councilors* 1923 A J CARLSON, *President*, C W GREENE, *Secretary*, J ERLANGER, *Treasurer*, C J WIGGERS, A B LUCKHARDT, J A E EYSTER, J R MURLIN, *Councilors* 1924 A J CARLSON, *President*, W J MEEK, *Secretary*, C K DRIVER, *Treasurer*, A B LUCKHARDT, J A E EYSTER,

J R MURLIN, W E GARREY, Councilors 1925 A J CARLSON, President, W J MEEK, Secretary, C K DRINKER, Treasurer, J A E EASTER, J R MURLIN, W E GARREY, JOSEPH ERLANGER, Councilors 1926 J ERLANGER, President, W J MEEK, Secretary, A FORBES, Treasurer, J R MURLIN, W E GARREY, A B LUCKHARDT, C J WIGGERS, Councilors 1927 J ERLANGER, President, W J MEEK, Secretary, A FORBES, Treasurer, W E GARREY, A B LUCKHARDT, C J WIGGERS, R GESELL, Councilors 1928 J ERLANGER, President, W J MEEK, Secretary, A FORBES, Treasurer, A B LUCKHARDT, C J WIGGERS, R GESELL, A J CARLSON, Councilors 1929 W J MEEK, President, ALFRED C REDFIELD, Secretary, A FORBES, Treasurer, C J WIGGERS, R GESELL, A J CARLSON, J R MURLIN, Councilors 1930 W J MEEK, President, ARNO B LUCKHARDT, Secretary, A FORBES, Treasurer, R GESELL, A J CARLSON, J R MURLIN, E G MARTIN, Councilors 1931 W J MEEK, President, ARNO B LUCKHARDT, Secretary, ALEXANDER FORBES, Treasurer, A J CARLSON, J R MURLIN, E G MARTIN, JOHN TAIT, Councilors 1932 ARNO B LUCKHARDT, President, FRANK C MANN, Secretary, ALEXANDER FORBES, Treasurer, E G MARTIN, W J MEEK, J R MURLIN, JOHN TAIT, Councilors 1933 ARNO B LUCKHARDT, President, FRANK C MANN, Secretary, ALEXANDER FORBES, Treasurer, HERBERT S GASSER, ERNEST G MARTIN, W J MEEK, JOHN TAIT, Councilors 1934 CHARLES W GREENE, President, FRANK C MANN, Secretary, ALEXANDER FORBES, Treasurer, HERBERT S GASSER, ARNO B LUCKHARDT, W J MEEK, JOHN TAIT, Councilors 1935 FRANK C MANN, President, ANDREW C IVY, Secretary, ALEXANDER FORBES, Treasurer, CHARLES H BEST, HERBERT S GASSER, ARNO B LUCKHARDT, W J MEEK, Councilors 1936 FRANK C MANN, President, ANDREW C IVY, Secretary, WALLACE O FENN, Treasurer, CHARLES H BEST, PHILIP BARD, HERBERT S GASSER, ARNO B LUCKHARDT, Councilors 1937 WALTER E GARREY, President, ANDREW C IVY, Secretary, WALLACE O FENN, Treasurer, CHARLES H BEST, PHILIP BARD, HERBERT S GASSER, ARNO B LUCKHARDT, Councilors 1938 WILLIAM T PORTER, Honorary President, WALTER E GARREY, President, ANDREW C IVY, Secretary, WALLACE O FENN, Treasurer, ARNO B LUCKHARDT, CHARLES H BEST, PHILIP BARD, HERBERT S GASSER, Councilors 1939 ANDREW C IVY, President, PHILIP BARD, Secretary, WALLACE O FENN, Treasurer, CHARLES H BEST, HERBERT S GASSER, ARNO B LUCKHARDT, MAURICE B VISSCHER, Councilors 1940 ANDREW C IVY, President, PHILIP BARD, Secretary, CARL J WIGGERS, Treasurer, CHARLES H BEST, HERBERT S GASSER, ARNO B LUCKHARDT, MAURICE B VISSCHER, Councilors 1941 PHILIP

BARD, President, CARL J WIGGERS, Secretary, HAMILTON DAVIS, Treasurer, CHARLES H BEST, ARNO B LUCKHARDT, MAURICE B VISSCHER, HIRAM E ESSLER, Councilors 1942, 1943, 1944, 1945 PHILIP BARD, President, WALLACE O FENN, Secretary, HAMILTON DAVIS, Treasurer, CHARLES H BEST, MAURICE B VISSCHER, HIRAM E ESSLER, W F HAMPTON, Councilors

CONSTITUTION

I

1 This Society shall be named "THE AMERICAN PHYSIOLOGICAL SOCIETY, INCORPORATED"

2 The Society is instituted to promote the advance of Physiology and to facilitate personal intercourse between American Physiologists

II

1 The Society shall consist of members and honorary members

2 Any person who has conducted and published meritorious original researches in Physiology and who is a resident of North America shall be eligible for membership in the Society

3 Members who have been relieved by the Council of the payment of the annual assessment shall retain all the rights of members

4 Distinguished men of science who have contributed to the advance of Physiology shall be eligible for election as honorary members of the Society. Honorary members shall pay no membership fee. They shall have the right of attending the meetings of the Society, and of taking part in its scientific discussions, but they shall have no vote

III

1 The management of the Society shall be vested in a Council consisting of the President, Secretary, and Treasurer and four other members to be chosen by ballot at each annual meeting. The President, Secretary, and Treasurer shall be elected for one year. The President shall be subject to only one reelection. The four additional members of the Council shall be elected for a term of four years and the term of office of one of these Councilors shall expire at the close of each annual meeting. The four additional members of the Council shall not succeed themselves. If the annual meeting is not held all the members of the Council shall continue in office until their successors are chosen in the prescribed manner and succession

2 The Council shall have power to fill all interim vacancies that may occur in its membership or in any Committee or board of the Society except those for which other provisions have been made

IV

1 At least a fortnight before the annual meeting the Secretary shall send to each member a notice of the place and time of each meeting, and shall make such other announcements as the Council shall direct

2 The annual assessment shall be determined by the Council, and shall be due in advance at the time of the annual meeting. No allocation or disbursement of funds of the Society shall be made except upon prior approval of the Council. Appropriations shall be made by the Council for the conduct of the necessary and appropriate business of the Society

3 Any member whose assessment is two years in arrears shall cease to be a member of the Society, unless at the next annual meeting he shall be reinstated by special vote of the Society, and it shall be the duty of the Treasurer to inform the Secretary that he may notify the said delinquent of his right to appeal to said meeting

4 Any member who has retired because of illness or age may, upon application to the Council be relieved from payment of the annual assessment

V

1 Meetings of the Society for the conduct of business and the presentation of papers and demonstrations shall be held annually except for national emergencies or other exceptional circumstances when the Council may cancel the proposed meeting. The time and place of such meetings shall be determined by the Council in consultation with the Executive Committee of the Federation of American Societies for Experimental Biology

2 Special meetings may be held at such times and places as the Council may determine

VI

1 Proposed amendments to the Constitution must be brought up at one meeting for preliminary discussion and approval by a majority vote and cannot be adopted except by a two thirds vote at a business session at the next annual meeting. Notice of such changes shall be sent to all members at least two weeks prior to the meeting at which they are scheduled for adoption

2 At all business meetings of the Society twenty-five members shall form a quorum

3 By laws for the conduct of the Society may be adopted, altered, or repealed at any business meeting by two-thirds vote of the ballots cast

VII

1 The Council may, from the names of the candidates proposed in writing by at least two members of the Society, nominate candidates for

election to membership. The names of the candidates so nominated and a statement of their qualifications for membership signed by their proposers shall be available for inspection during the business sessions of the Society at which their election is considered. The candidates may be balloted for at any session of the same meeting and a majority vote shall elect. If an annual meeting is not held, the Council shall elect the candidates to membership subject to Society approval at the next annual meeting

2 Honorary members shall be proposed by the Council, and shall be elected by a majority ballot of the members present at an annual business session of the Society

VIII

1 If a majority of the Council shall decide that the interests of the Society require the expulsion of a member the Secretary shall send a notice of this decision to each member at least two weeks before the next annual meeting. At this meeting the Secretary shall, on behalf of the Council, propose the expulsion, and if two-thirds of the members present vote for it, the member shall be expelled, and his assessment for the current year shall be returned to him, and he shall cease to be a member of the Society

IX

1 The official organs of the Society shall be the American Journal of Physiology, the Physiological Reviews and such other publications as the Society shall establish. These the Society shall own and they shall be managed according to the provisions of Article X

X

1 The President of the Society shall appoint, in consultation with the Council and subject to the approval of the Society, three members of the Society to serve as members of a Board of Publication Trustees

2 The initial appointments shall be for one, two and three years. Thereafter, each member shall be appointed for three years, and shall be eligible for one immediate reappointment. He may be subsequently reappointed, but only after the lapse of at least one year between reappointments

3 The Board of Publication Trustees shall be vested with full power of the Society to control and manage, both editorially and financially, all of the publications owned in whole or in part by the Society, to appoint editorial boards, to appoint and compensate a Managing Editor, and to control all publication funds, none of which, however, may be diverted from support of publications of the Society except by consent of the Council

4 The Board of Publication Trustees shall make a full report to the Council at each annual meeting of the financial condition and publication policy of the Journals or other publications

BY-LAWS

1 All papers read before the Society shall be limited to a length of ten minutes. No person may orally present more than one paper. In case of joint authorship the name of the individual who will orally present the paper shall stand first.

2 Abstracts in duplicate, not to exceed two-hundred and fifty words in length, of all papers to be presented at the annual meeting of the Society shall be required by the Secretary for publication in the Federation Proceedings, in accordance with rules approved by the Council.

3 The Council shall upon the request of twenty-five members call a regional meeting of the Society

at any time and place, for the reading of papers and the promotion of personal intercourse. Such a request shall be made in writing at least six weeks before the proposed date of meeting. Such meeting shall be held in accordance with the Constitution and By-laws of the Society, and if the regular officers of the Society cannot be present the President shall appoint a committee from among the petitioners to conduct the meeting. The Committee through a Secretary chosen by them shall forward an account of the scientific proceedings of the meeting to the official Secretary of the Society for insertion in the minutes. The Secretary of the meeting shall also prepare and transmit to the official Secretary such abstracts of papers read as may be furnished him, and these abstracts shall be published in the Federation Proceedings in accordance with By-law No. 2.

4 No general business of the Society shall be transacted at such regional meetings.

THE AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, INCORPORATED

Founded December 6, 1906, Incorporated September 12, 1919

OFFICERS ELECTED 1946

President—A B HASTINGS, Harvard Medical School, Boston 15, Mass

Vice-President—H T CLARKE, 630 West 168th St, New York 32, N Y

Secretary—OTTO A BESSEY, Public Health Research Inst, City of New York, Foot of East 15th St, New York, N Y

Treasurer—E A EVANS, JR, Univ of Chicago, Chicago 37, Ill

Councilors-at-large—V DU VIGNEAUD, Cornell University Medical College, New York 21, N Y, C F CORI, Washington Univ School of Medicine, St Louis, 10, Missouri, A K BALLS, Enzyme Research Laboratory, Albany 6, Calif

Nominating Committee—W C ROSE, Chairman, E A DOISY, C G KING, C A ELVEHJEM, C F CORI, E G BALL, H A MATTILL, H B LEWIS, H J DEUEL, JR

PAST OFFICERS

1907 RUSSELL H CHITTENDEN, President, J J ABEL, Vice-President, W J GIES, Secretary, L B MENDEL, Treasurer, W JONES, W KOCH, J MARSHALL, T B OSBORNE, Councilors 1908 JOHN J ABEL, President, OTTO FOLIN, Vice-President, WM J GIES, Secretary, L B MENDEL, Treasurer, A B MACALLUM, A P MATHEWS, F G NOVY, Councilors 1909 OTTO FOLIN, President, T B OSBORNE, Vice-President, WM J GIES, Secretary, L B MENDEL, Treasurer,

J J ABEL, P A LEVENE, G LUSK, Councilors 1910 THOMAS B OSBORNE, President, L B MENDEL, Vice-President, A N RICHARDS, Secretary, WALTER JONES, Treasurer, A B MACALLUM, A P MATHEWS, V C VAUGHAN, Councilors 1911 LAFAYETTE B MENDEL, President, A B MACALLUM, Vice-President, A N RICHARDS, Secretary, WALTER JONES, Treasurer, WM J GIES, A S LOEVENHART, P A SHAFFER, Councilors 1912 ARCHIBALD B MACALLUM, President, G LUSK, Vice-President, A N RICHARDS, Secretary, WALTER JONES, Treasurer, H P ARMSBY, L B MENDEL, H G WELLS, Councilors 1913 ARCHIBALD B MACALLUM, President, G LUSK, Vice-President, P A SHAFFER, Secretary, D D VAN SLYKE, Treasurer, H P ARMSBY, L B MENDEL, H G WELLS, Councilors 1914 GRAHAM LUSK, President, C L ALSBERG, Vice-President, P A SHAFFER, Secretary, D D VAN SLYKE, Treasurer, J J ABEL, A B MACALLUM, T B OSBORNE, Councilors 1915 WALTER JONES, President, C L ALSBERG, Vice-President, P A SHAFFER, Secretary, D D VAN SLYKE, Treasurer, OTTO FOLIN, G LUSK, L B MENDEL, Councilors 1916 WALTER JONES, President, F P UNDERHILL, Vice-President, S R BENEDICT, Secretary, D D VAN SLYKE, Treasurer, OTTO FOLIN, A B MACALLUM, P A SHAFFER, Councilors 1917 CARL L ALSBERG, President, A P MATHEWS, Vice-President, S R BENEDICT, Secretary, H C BRADLEY, Treasurer, L J HENDERSON, P A SHAFFER, F P UNDERHILL, Councilors 1918

CARL L. AISBERG, President, A. P. MATHEWS, Vice-President, S. R. BENEDICT, Secretary, H. C. BRADLEY, Treasurer, W. J. GIPS, ANDREW HUNTER, E. V. MCCOLLUM, Councilors 1919 STANLEY R. BENEDICT, President, D. D. VAN SLYKE, Vice-President, V. C. MYERS, Secretary, H. C. BRADLEY, Treasurer, ANDREW HUNTER, E. V. MCCOLLUM, L. B. MENDEL, Councilors 1920 STANLEY R. BENEDICT, President, D. D. VAN SLYKE, Vice-President, V. C. MYERS, Secretary, H. C. BRADLEY, Treasurer, OTTO FOLIN, WALTER JONES, L. B. MENDEL, Councilors 1921 DONALD D. VAN SLYKE, President, P. A. SHAFFER, Vice-President, V. C. MYERS, Secretary, H. C. BRADLEY, Treasurer, S. R. BENEDICT, OTTO FOLIN, WALTER JONES, Councilors 1922 DONALD D. VAN SLYKE, President, P. A. SHAFFER, Vice-President, V. C. MYERS, Secretary, W. R. BLOOR, Treasurer, S. R. BENEDICT, H. C. BRADLEY, A. P. MATHEWS, Councilors 1923 PHILIP A. SHAFFER, President, H. C. SHERMAN, Vice-President, V. C. MYERS, Secretary, W. R. BLOOR, Treasurer, H. C. BRADLEY, ANDREW HUNTER, A. P. MATHEWS, Councilors 1924 PHILIP A. SHAFFER, President, HENRY C. SHERMAN, Vice-President, D. WRIGHT WILSON, Secretary, WALTER R. BLOOR, Treasurer, OTTO FOLIN, ANDREW HUNTER, VICTOR C. MYERS, Councilors 1925 HENRY C. SHERMAN, President, EDWARD C. KENDALL, Vice-President, D. WRIGHT WILSON, Secretary, WALTER R. BLOOR, Treasurer, OTTO FOLIN, LAFAYETTE B. MENDEL, PHILIP A. SHAFFER, Councilors 1926 EDWARD C. KENDALL, President, ELMER V. MCCOLLUM, Vice-President, FRED C. KOCH, Secretary, GLENN E. CULLEN, Treasurer, J. B. COLLIP, EDWARD A. DOISY, ALBERT P. MATHEWS, Councilors 1927 E. V. MCCOLLUM, President, W. R. BLOOR, Vice-President, D. WRIGHT WILSON, Secretary, G. E. CULLEN, Treasurer, E. A. DOISY, F. C. KOCH, D. D. VAN SLYKE, Councilors 1928 E. V. MCCOLLUM, President, W. R. BLOOR, Vice-President, D. WRIGHT WILSON, Secretary, G. E. CULLEN, Treasurer, W. M. CLARK, F. C. KOCH, D. D. VAN SLYKE, Councilors 1929 W. R. BLOOR, President, H. C. BRADLEY, Vice-President, H. B. LEWIS, Secretary, G. E. CULLEN, Treasurer, W. M. CLARK, C. L. A. SCHMIDT, P. A. SHAFFER, Councilors 1930 W. R. BLOOR, President, H. C. BRADLEY, Vice-President, H. B. LEWIS, Secretary, G. E. CULLEN, Treasurer, W. M. CLARK, P. A. SHAFFER, D. W. WILSON, Councilors 1931 H. C. BRADLEY, President, W. M. CLARK, Vice-President, H. B. LEWIS, Secretary, C. H. FISKE, Treasurer, W. C. ROSE, P. A. SHAFFER, D. W. WILSON, Councilors 1932 H. C. BRADLEY, President, W. M. CLARK, Vice-President, H. B. LEWIS, Secretary, C. H. FISKE, Treasurer, P. E. HOWE, W. C. ROSE, D. W. WILSON, Councilors 1933 W. M. CLARK, President, H. B. LEWIS, Vice-Presi-

dent, H. A. MATTILL, Secretary, C. H. FISKE, Treasurer, H. C. BRADLEY, P. E. HOWE, W. C. ROSE, Councilors 1934 W. M. CLARK, President, H. B. LEWIS, Vice-President, H. A. MATTILL, Secretary, C. H. FISKE, Treasurer, H. C. BRADLEY, E. A. DOISY, P. E. HOWE, Councilors 1935 H. B. LEWIS, President, G. E. CULLEN, Vice-President, H. A. MATTILL, Secretary, C. H. FISKE, Treasurer, H. C. BRADLEY, J. B. COLLIP, E. A. DOISY, Councilors 1936 H. B. LEWIS, President, G. E. CULLEN, Vice-President, H. A. MATTILL, Secretary, A. B. HASTINGS, Treasurer, J. B. COLLIP, E. A. DOISY, W. C. ROSE, Councilors 1937 G. E. CULLEN, President, W. C. ROSE, Vice-President, H. A. MATTILL, Secretary, A. B. HASTINGS, Treasurer, E. A. DOISY, H. B. LEWIS, H. B. VICKERY, Councilors 1938 G. E. CULLEN, President, W. C. ROSE, Vice-President, CHARLES G. KING, Secretary, A. B. HASTINGS, Treasurer, H. B. LEWIS, H. A. MATTILL, H. B. VICKERY, Councilors 1939 W. C. ROSE, President, R. J. ANDERSON, Vice-President, CHARLES G. KING, Secretary, A. B. HASTINGS, Treasurer, H. B. LEWIS, H. A. MATTILL, G. E. CULLEN, Councilors 1940 WILLIAM C. ROSE, President, RUDOLPH J. ANDERSON, Vice-President, CHARLES G. KING, Secretary, A. B. HASTINGS, Treasurer, H. A. MATTILL, GLENN E. CULLEN, E. A. DOISY, Councilors 1941 R. J. ANDERSON, President, E. A. DOISY, Vice-President, A. K. BALLS, Secretary, W. C. STADIE, Treasurer, H. B. LEWIS, W. C. ROSE, Councilors 1942 R. J. ANDERSON, President, E. A. DOISY, Vice-President, A. K. BALLS, Secretary, W. C. STADIE, Treasurer, W. C. ROSE, C. A. KING, H. Y. CLARKE, Councilors 1943 E. A. DOISY, President, A. B. HASTINGS, Vice-President, A. K. BALLS, Secretary, W. C. STADIE, Treasurer, W. C. ROSE, H. T. CLARKE, R. J. ANDERSON, Councilors 1944 E. A. DOISY, President, A. B. HASTINGS, Vice-President, A. K. BALLS, Secretary, W. C. STADIE, Treasurer, R. J. ANDERSON, H. T. CLARKE, V. DU VIGNEAUD, Councilors 1945 A. B. HASTINGS, President, H. T. CLARKE, Vice-President, A. K. BALLS, Secretary, W. C. STADIE, Treasurer, R. J. ANDERSON, C. F. CORI, V. DU VIGNEAUD, Councilors

CONSTITUTION

FROM THE ARTICLES OF INCORPORATION

1 The name of the proposed corporation is "AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, INCORPORATED"

2 The purposes for which this corporation is formed are to further the extension of biochemical knowledge and to facilitate personal intercourse between American investigators in biological chemistry

BY-LAWS

ARTICLE I—*Membership*

SECTION 1 *Eligibility for Membership*—Qualified investigators who have conducted and published meritorious original investigations in biological chemistry shall be eligible for membership in the Society

SEC 2 *Nomination*—Nominations for membership shall be made and seconded by members of the Society on blanks furnished by the Secretary. Nominations shall be submitted to the Council who shall determine eligibility and make recommendation to the Society at a regular meeting

SEC 3 *Election to Membership*—A A nominee for membership may be voted for by ballot at any meeting of the Society after Council has reported its findings on his eligibility. The eligible candidate shall be reported by the Council as "eligible" or as "eligible and indorsed." B A majority of the ballots cast shall elect

SEC 4 *Forfeiture*—A Any member who may grant the use of his name for (a) the advertisement of a patent medicine, a proprietary food preparation, or any other commercial article of doubtful value to the public or possibly harmful to the public health, or (b) who may concede its use for the purpose of encouraging the sale of individual samples (of any such product) that he has not examined, shall forfeit his membership

B The Council shall have authority to announce forfeiture of membership, provided that the copy of the charges, together with a written notice of a hearing thereon by the Council at a place and time specified in such notice, shall have been delivered to the member charged with violating the preceding section either personally or mailed to him at his last known address at least thirty days before the date of such hearing

SEC 5 *Expulsion*—Upon the recommendation of the Council any member may be expelled by a majority vote of the total membership at a meeting of the Society, provided that a copy of the charges against him, together with a written notice of a hearing thereon by the Council at a place and time specified in such notice shall have been delivered to him personally or mailed to him at his last known address at least thirty days before the date of such hearing

ARTICLE II—*Meetings and Quorum*

SECTION 1 *Annual*—The annual meeting of the Society shall be held on the date fixed by the Certificate of Incorporation

SEC 2 *Special*—A special meeting may be called at any time by the President, or in case of his absence or disability, by the Vice-President, and must be called at the request of a majority of the Council or fifteen members of the Society. A notice

specifying the purpose of such meeting shall be mailed to each member at least ten days previous thereto. The Council shall select the places at which meetings shall be held

SEC 3 *Quorum*—Fifteen members shall constitute a quorum at all meetings of the Society, but in absence of a quorum any number shall be sufficient to adjourn to a fixed date

ARTICLE III—*Officials*

SECTION 1 *Officers*—The officers shall be a President, a Vice-President, a Secretary, and a Treasurer, who shall be elected annually by the members of the Society

SEC 2 *Council*—A The officers so elected and three additional members, one of whom shall be elected at each annual meeting of the Society to serve a three year term, shall constitute the Board of Directors of the corporation and shall be known as "The Council." (When this provision is first put into effect three members will need to be elected for a one, a two and a three year period.)

B No two members of the Council may be from the same institution, and none of the officers so elected shall be eligible for re-election for more than two years except the Secretary and Treasurer, who shall be eligible for re-election for five years. The three additional members of the Council shall be ineligible for re-election (until after the lapse of one year)

SEC 3 *Duties of Officers*—The powers and duties of the officers elected by the Society shall be such as usually devolve upon their respective positions

SEC 4 *Assistant Treasurer*—A The Council may from time to time appoint a trust company, or some member of the Society, to serve during the pleasure of the Council as Assistant Treasurer, and to act as depositary of the investments and income of the "Christian A. Herter Memorial Fund" and of such other funds as the Society may from time to time commit to its or his charge

B The Assistant Treasurer shall have and exercise the following powers and duties, viz, the custody and safe-keeping of securities and cash belonging to the "Christian A. Herter Fund" and the collection of income and other moneys due to the Fund, with power to receipt for the same and to endorse for deposit all checks payable to the Society or the Treasurer, or to the Journal of Biological Chemistry for income or other moneys due to the Fund, the investment or reinvestment of the capital of the Fund, subject to the approval of the Council, the disbursement of principal under the direction of the Council and the disbursement of income under the direction of the Editorial Board of the Journal of Biological Chemistry, such disbursement to be made under a resolution of the Council or Board, or with the approval of two members of either the Council or Board,

as the case may be. The Assistant Treasurer shall keep books of account and render statements, annually or oftener upon the request of the Council or Board setting forth the condition of the Fund and the receipts and disbursements since the date of the preceding statement.

ARTICLE IV—*The Council*

SECTION 1 Powers—The general management of the Society during the intervals between meetings shall be vested in the Council, which shall regularly perform the ordinary duties of an executive committee and possess all the powers conferred upon the Board of Directors of a membership corporation by the Membership Corporation Law of the State of New York.

SEC 2 Reports—The Council shall report to the Society as promptly as possible its findings on the eligibility of candidates for membership, and on all charges of a violation of these By-Laws.

SEC 3 Journal of Biological Chemistry—The Council shall have power to appoint the persons to act as proxies for the Society at all meetings of the stockholders of the "Journal of Biological Chemistry" (a corporation) of which all the stock is owned by the Society, and also to designate the persons to be elected as Directors of such corporation.

SEC 4 Herter Fund—It shall be the duty of the Council to see that the "Christian A. Herter Memorial Fund" is administered in accordance with the terms of the Trust Agreement, dated May 16, 1911, executed by the Journal of Biological Chemistry and the donors of said Fund.

ARTICLE V—*Nominating Committee*

SECTION 1 Membership—A The nominating Committee shall consist of nine members from nine different institutions elected at each annual meeting to serve for the ensuing year. Members who have served on the Nominating Committee for two consecutive years shall be ineligible for re-election until after the lapse of one year.

B The member of the Nominating Committee who is elected to the Committee by the largest number of votes shall become Chairman and Secretary of the Committee.

SEC 2 Nomination of Officials—A The Nominating Committee shall make at least one nomination for each of the four offices and for each of the three additional positions in the Council to be filled by vote of the members.

B The nominations by the Nominating Committee must be transmitted to the Secretary at least one month before the annual meeting at which they are to be considered.

C The Secretary shall send to every member, at least two weeks before the annual meeting, two copies of the list of nominees presented to him by

the Nominating Committee and at the same time shall notify all the members that they may vote by proxy.

D At the opening of the first executive session of the ensuing annual meeting the Secretary shall formally present the regular nominations for the Nominating Committee.

E Additional nominations for the offices and for membership in the Council may be made by any member at the opening of the first executive session of any annual meeting.

F Nominations for membership on the Nominating Committee shall be made by or for individual members, either in person or by proxy, and not otherwise, at the opening of the first executive session of any annual meeting.

SEC 3 Election of Officials—A The Secretary shall receive and present to the tellers, appointed by the President to take charge of the election, all signed ballots forwarded by absent members. When such ballots are presented to the tellers the Secretary shall announce the names of the members voting by proxy, and he shall record the same names in the minutes of the meeting.

B All elective officials shall be selected by ballot at the close of the first executive session of each annual meeting.

C A majority of the votes cast shall be necessary to elect an official.

D Elective officials shall take office on July 1st following the annual meeting.

SEC 4 Filling of Vacancies—A The Nominating Committee shall fill all vacancies in elective positions except such as may occur at a meeting of the Society.

B The President of the Society shall fill all vacancies in appointive positions.

ARTICLE VI—*Financial*

SECTION 1 Dues—Annual assessments shall be determined by majority vote at the annual meetings, upon the recommendation of the Council, and shall be due January 15th in each year. Members who have reached the age of 65 years, or who have become incapacitated, may, by vote of the Council, be exempted from the payment of dues.

SEC 2 Expenditures—No expenditures from the general funds of the Society except those required in the performance of the ordinary official duties shall be made except by vote of the Society or the Council, but this section shall not apply to expenditures from the "Christian A. Herter Memorial Fund."

SEC 3 Privileges of Membership Begin with Payment of Dues—Candidates for membership, if elected, shall not be entitled to any of the privileges of membership, before they pay the dues of the fiscal year succeeding their election.

SEC 4 Penalty for Non-Payment of Dues—A

Members in arrears for dues for a period of three consecutive years shall thereupon forfeit their membership

B Delinquent members may be reinstated by the Council provided all indebtedness to the Society is liquidated

SEC 5 *Herter Fund*—The "Christian A Herter Memorial Fund" shall be held and invested separately from the general funds of the Society and the income thereof shall be expended under the direction of the Editorial Board exclusively for the maintenance and support of the Journal of Biological Chemistry, subject to the supervision and control of the Editorial Committee in accordance with the terms of the Trust Agreement mentioned in ARTICLE IV, SECTION 4, and the provisions of ARTICLE VII of the By-Laws

ARTICLE VII—*Journal of Biological Chemistry*

SECTION 1 *Editorial Committee*—There shall be an Editorial Committee consisting of nine members of the Society who shall be nominated by the Nominating Committee and elected by the Society in the same manner as officers. The nine members first elected shall divide themselves by lot into three classes of three in each class, to serve for two, four, and six years respectively, and thereafter three members shall be elected at each alternate annual meeting of the Society to succeed the members of the outgoing class and to serve for a term of six years. Members of the Committee shall be eligible to re-election

SEC 2 *Powers of Committee*—The Committee shall have power to elect an Editorial Board and shall have final authority in matters pertaining to the general policy of the Journal

SEC 3 *Editorial Board*—The members of the Board shall hold office until their successors are elected and shall appoint a Managing Editor from among their own number who shall have direct responsibility and authority for the active editorial conduct of the Journal, and who shall have discretionary power in arranging the details as to the conduct of the Journal. The expenditures of the income of the "Christian A Herter Memorial Fund" shall be under the direction of the Board, and the approval of any two members of the Board shall be a sufficient warrant to authorize payments from such income

ARTICLE VIII—*Papers on Scientific Subjects*

SECTION 1 *Presentation of Papers*—The Secre-

tary shall request each member who signifies his intention of reading a paper at any session to specify the length of time which its presentation will require. The time thus specified shall be printed on the official program, and the presiding officer shall have no authority to extend it unless a majority of the members present signify their wish to the contrary. In the absence of any specification of time required not more than ten minutes shall be allotted for the reading of any one paper

SEC 2 *Number of Papers*—No member shall be permitted to present more than one paper, either alone or in collaboration, until every member shall have had the opportunity of presenting one paper

ARTICLE IX—*Corporate Seal*

SECTION 1 The corporate seal of the corporation shall be a circle surrounded by the words, "AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS," and including the word, "INCORPORATED "

ARTICLE X—*Amendments*

SECTION 1 *Amendments*—These By-Laws, after having been approved by the Council, and adopted by the Society at its first annual meeting, shall not be amended except as hereinafter provided

SEC 2 *Manner of Presentation*—Proposed amendments to the By-Laws must be sent to the Secretary at least one month before the date of the meeting at which they are to be considered and must be indorsed in writing by at least three members

SEC 3 *Notice of Intended Amendments*—The Secretary shall give every member notice of proposed amendments at least two weeks before the meeting at which they are to be considered and shall notify all members that they may vote by proxy

SEC 4 *Adoption of Amendments*—A The Secretary shall receive and present to the tellers appointed by the President all signed ballots forwarded by absent members. When such ballots are presented to the tellers, the Secretary shall announce the names of members voting by proxy, and he shall record the same names in the minutes of the meeting

B Votes upon amendments shall be cast at the opening of the second executive session of the meeting at which they are considered

C Affirmative votes from three-fifths of the members voting shall be required for the adoption of an amendment

AMERICAN SOCIETY FOR PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, INCORPORATED

Founded December 28, 1908, Incorporated June 19, 1933

OFFICERS ELECTED 1916

President—MAURICE H. SEEVERS, University of Michigan Medical School, Ann Arbor, Mich

Vice President—H. B. VAN DYKE, College of Physicians and Surgeons, Columbia Univ., New York

Secretary—HARVEY B. HAAG, Medical College of Virginia, Richmond, Va

Treasurer—MCKENNA CATTELL, Cornell University Medical College, New York 21, N. Y.

Council—HAMPTON H. ANDERSON, Univ. of California Medical School San Francisco, JOHN C. KRANTZ, JR., University of Maryland, Baltimore, MAURICE H. SEEVERS, H. B. VAN DYKE, HARVEY B. HAAG, MCKENNA CATTELL

Membership Committee—CARL A. DRAGSTEDT (term expires 1947) Northwestern Univ. Medical School, Chicago, Ill., CARL F. SCHMIDT (term expires 1948) Univ. of Pennsylvania Medical School, Philadelphia 4, Pa., CHARLES M. GRUBER (term expires 1949) Jefferson Medical College, 1025 Walnut St., Philadelphia, Pa.

Nominating Committee—K. K. CHEN, Chairman, ALFRED GILMAN, P. K. KNOEFEL, CARL PFEIFFER, ROBERT A. WOODBLIN

PAST OFFICERS

1909 J. J. ABEL, President, REID HUNT, Secretary, A. S. LOEVENHART, Treasurer, S. J. MELTZER, T. SOLLMANN, C. W. EDMUNDS, A. C. CRAWFORD, Councilors 1910 J. J. ABEL, President, REID HUNT, Secretary, A. S. LOEVENHART, Treasurer, A. C. CRAWFORD, G. B. WALLACE, Councilors 1911 J. J. ABEL, President, REID HUNT, Secretary, A. S. LOEVENHART, Treasurer, G. B. WALLACE, W. DEB. MACNIDER, Councilors 1912 J. J. ABEL, President, J. AUER, Secretary, A. S. LOEVENHART, Treasurer, G. B. WALLACE, REID HUNT, Councilors 1913 T. SOLLMANN, President, J. AUER, Secretary, A. S. LOEVENHART, Treasurer, J. J. ABEL, W. DEB. MACNIDER, Councilors 1914 T. SOLLMANN, President, J. AUER, Secretary, W. DEB. MACNIDER, Treasurer, J. J. ABEL, A. S. LOEVENHART, Councilors 1915 T. SOLLMANN, President, J. AUER, Secretary, W. DEB. MACNIDER, Treasurer, WORTH HALE, D. E. JACKSON, Councilors 1916 REID HUNT, President, J. AUER, Secretary, W. DEB. MACNIDER, Treasurer, A. D. HIRSCHFELDER, G. B. ROTH, Councilors 1917 REID HUNT, President, L. G. ROWNTREE, Secretary, W. DEB. MACNIDER, Treasurer, J. AUER, CARL VOEGTLIN, Councilors 1918 REID HUNT, President, E. D. BROWN, Secre-

tary, W. DEB. MACNIDER, Treasurer, HUGH MCGUIGAN, CARL VOEGTLIN, Councilors 1919 A. S. LOEVENHART, President, E. D. BROWN, Secretary, W. DEB. MACNIDER, Treasurer, REID HUNT, E. K. MARSHALL, JR., Councilors 1920 A. S. LOEVENHART, President, E. D. BROWN, Secretary, W. DEB. MACNIDER, Treasurer, D. E. JACKSON, E. K. MARSHALL, JR., Councilors 1921 C. W. EDMUNDS, President, E. D. BROWN, Secretary, HUGH MCGUIGAN, Treasurer, JOHN AUER, J. P. HANZLIK, Councilors 1922 C. W. EDMUNDS, President, E. D. BROWN, Secretary, HUGH MCGUIGAN, Treasurer, J. P. HANZLIK, H. G. BARBOUR, Councilors 1923 C. W. EDMUNDS, President, E. D. BROWN, Secretary, HUGH MCGUIGAN, Treasurer, J. P. HANZLIK, H. G. BARBOUR, Councilors 1924 JOHN AUER, President, E. D. BROWN, Secretary, A. L. TATUM, Treasurer, J. P. HANZLIK, H. G. BARBOUR, Councilors 1925 JOHN AUER, President, E. D. BROWN, Secretary, A. L. TATUM, Treasurer, H. G. BARBOUR, W. DEB. MACNIDER, Councilors 1926 JOHN AUER, President, E. D. BROWN, Secretary, A. L. TATUM, Treasurer, H. G. BARBOUR, W. DEB. MACNIDER, Councilors 1927 CARL VOEGTLIN, President, E. D. BROWN, Secretary, A. L. TATUM, Treasurer, V. E. HENDERSON, C. W. EDMUNDS, Councilors 1928 CARL VOEGTLIN, President, E. D. BROWN, Secretary, A. L. TATUM, Treasurer, V. E. HENDERSON, C. W. EDMUNDS, Councilors 1929 CARL VOEGTLIN, President, E. D. BROWN, Secretary, O. H. PLANT, Treasurer, V. E. HENDERSON, C. W. EDMUNDS, Councilors 1930 GEORGE B. WALLACE, President, E. D. BROWN, Secretary, O. H. PLANT, Treasurer, H. G. BARBOUR, C. M. GRUBER, Councilors 1931 GEORGE B. WALLACE, President, VELIEN E. HENDERSON, Secretary, O. H. PLANT, Treasurer, PAUL D. LAMSON, WILLIAM DEB. MACNIDER, Councilors 1932 WM. DEB. MACNIDER, President, A. N. RICHARDS, Vice-President, V. E. HENDERSON, Secretary, O. H. PLANT, Treasurer, G. B. ROTH, A. L. TATUM, Councilors 1933 WM. DEB. MACNIDER, President, A. L. TATUM, Vice-President, V. E. HENDERSON, Secretary, O. H. PLANT, Treasurer, C. M. GRUBER, G. B. ROTH, Councilors 1934 R. A. HATCHER, President, A. L. TATUM, Vice-President, E. M. K. GEILING, Secretary, O. H. PLANT, Treasurer, WM. DEB. MACNIDER, R. L. STEHLE, Councilors 1935 V. E. HENDERSON, President, O. H. PLANT, Vice-President, E. M. K. GEILING, Secretary, C. M. GRUBER, Treasurer, FLOYD DEEDS, M. S. DOOLEY, Councilors 1936 V. E. HENDERSON, Presi-

dent, O H PLANT, Vice-President, E M K GEILING, Secretary, C M GRUBER, Treasurer, C W EDMUNDS, G B WALLACE, Councilors 1937 A L TATUM, President, F M K GLIING, Vice-President, G P GRABFIELD, Secretary, C M GRUBER, Treasurer, V E HENDERSON, M H SEEVERS, Councilors 1938 A L TATUM, President, E M K GEILING, Vice-President, G P GRABFIELD, Secretary, C M GRUBER, Treasurer, E K MARSHALL, JR, C F SCHMIDT, Councilors 1939 O H PLANT, President, E M K GEILING, Vice-President, G P GRABFIELD, Secretary, E E NELSON, Treasurer, A L TATUM, C A DRAGSTEDT, Councilors 1940 E M K GEILING, President, C F SCHMIDT, Vice-President, G PHILIP GRABFIELD, Secretary, E E NELSON, Treasurer, B H ROBBINS, C H THIENFIS, Councilors 1941 E M K GEILING, President, C F SCHMIDT, Vice-President, RAYMOND N BIETER, Secretary, E E NELSON, Treasurer, E G GROSS, R G SMITH, Councilors 1942 E K MARSHALL, JR, President, CARL A DRAGSTEDT, Vice-President, RAYMOND N BIETER, Secretary, E E NELSON, Treasurer, McK CATTELL, R G SMITH, Councilors 1943 E K MARSHALL, JR, President, CARL A DRAGSTEDT, Vice-President, RAYMOND N BIETER, Secretary, E E NELSON, Treasurer, McK CATTELL, R G SMITH, Councilors 1944, 1945 E E NELSON, President, C M GRUBER, Vice-President, R N BIETER, Secretary, McK CATTELL, Treasurer, HARRY BECKMAN, NATHAN B EDDY, Councilors

CONSTITUTION

ARTICLE I—Name

The name of this organization shall be the "AMERICAN SOCIETY FOR PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, INCORPORATED"

ARTICLE II—Objects

The purpose of this Society shall be to promote these branches of science and to facilitate personal intercourse between investigators who are actively engaged in research in these fields

ARTICLE III—Membership

SECTION 1 Any person who has conducted and published a meritorious investigation in pharmacology or experimental therapeutics, and who is an active investigator in one of these fields, shall be eligible to membership, subject to the conditions of the other sections of Article III

SEC 2 A Candidates for membership to this Society shall be proposed by two members who are not members of the Council. The names so proposed shall be sent to the Secretary at least three months prior to the Annual Meeting

B The Membership Committee shall investigate

the qualifications of the candidates and report to the Council

C Candidates reported upon by the Membership Committee to the Council may be recommended for admission by the Council only provided they have been approved by four-fifths of the combined membership of the Membership Committee and the Council

D The names of the candidates recommended for admission by the Council shall be posted by the Secretary not later than the day preceding the election for members

E The election of members shall be by individual ballot, one opposing vote in every eight cast shall be sufficient to exclude a candidate from membership

SEC 3 Forfeiture of Membership

A Any member whose assessment is three years in arrears shall cease to be a member of the Society, unless he shall be reinstated by a special vote of the Council, and it shall be the duty of the Treasurer to inform the Secretary that he may notify the said delinquent of his right to appeal to the Council

B If the Council shall decide that it is for the best interests of the Society that a member be expelled, the member shall be notified and given an opportunity of a hearing before the Council. Upon the recommendation of the Council the member then may be expelled by a three-fourths vote of those present at a regular meeting of the Society

SEC 4 Honorary Members

A Distinguished men of science who have contributed to the advance of pharmacology or experimental therapeutics shall be eligible for election as honorary members of the Society

B Nominations for honorary members shall take the same course as nominations for ordinary members (Art III, Sec 2), but their election shall require the unanimous vote of the members present at the election

C Honorary members shall pay no membership fee. They shall have the right to attend all meetings of the Society, and to take part in its discussions, but they shall have no vote

D The conditions for continuation of membership shall be the same for honorary as for ordinary members (Art III, Sec 3), except that forfeiture for arrears of fees does not apply to honorary members

ARTICLE IV—Officers and Elections

SECTION 1 The management of the Society shall be vested in a Council of six officers, consisting of a President, a Vice-President, a Secretary, a Treasurer and two additional members

SEC 2 There shall be a Membership Committee consisting of three members, and a Nominating

Committee consisting of five members No two members of either Committee shall be from the same institution

SEC 3 Members of the Council shall serve for one year but they shall be eligible for re election

SEC 4 The election of the Membership Committee shall be held annually at the time when the election of officers occurs At the first meeting of the Society under this Constitution, one member shall be elected to serve on the Committee for three years, one for two years, and one for one year, and subsequently one member shall be elected each year to serve for a period of three years

SEC 5 A Members of the Nominating Committee shall serve for one year They are eligible for re-election, but shall not hold membership in the Committee for more than two consecutive years

B The Nominating Committee shall make at least one nomination for each office and for position on the Membership Committee to be filled by vote of the members The nominations so made shall be transmitted to the Secretary and by him in turn to the members, at least one month before the annual meeting Additional nominations may be made by any member at the time of the annual meeting

C Nominations for membership on the Nominating Committee shall be made by individual members at the time of the annual election The five nominees who receive the highest number of votes shall be declared elected The Nominating Committee shall select its own chairman who shall also serve as secretary to the Committee

SEC 6 The election of officers shall be held at the close of the first session of the annual meeting In voting there shall be a ballot in regular order for each office to be filled, and the majority of the votes cast shall be necessary to a choice

SEC 7 Such vacancies as may occur in the offices and in the various committees in the interval between annual meetings shall be filled by a majority vote of the Council

ARTICLE V—Meetings

SECTION 1 The annual meeting of the Society shall be held at a time and place determined by the Council in consultation with the Executive Committee of the Federation of American Societies for Experimental Biology

SEC 2 Special meetings may be held at such times and places as the Council may determine

SEC 3 At least four weeks before the annual meeting the Secretary shall send to each member a notice of the time and place of such meeting and shall make such announcements as the Council may direct

ARTICLE VI—Financial

SECTION 1 The annual assessment shall be determined by majority vote at the annual meetings, upon the recommendation of the Council, and shall be due in advance at the time of the meeting

SEC 2 Beyond the ordinary expenditures required by the routine business of the Society no money shall be disbursed save by the authority of the Council or Society

SEC 3 The treasurer shall make an annual report to the Society

SEC 4 In case any profits result to the Society from the Journal of Pharmacology and Experimental Therapeutics at the end of the financial year, such profits shall be kept in a special account, after deducting any sums expended by the Society during the year for the conduct of the Journal, and shall be held subject to the order of the Council on recommendation of the Editorial Board

ARTICLE VII—Quorum

Ten members shall constitute a quorum for the transaction of business

ARTICLE VIII—By-Laws

By-Laws shall be adopted, altered or repealed at any meeting by two thirds vote of the ballots cast

ARTICLE IX—Amendments

SECTION 1 Intended amendments to the Constitution shall be sent to the Secretary at least one month before the date of the meeting at which they are to be considered, and must be indorsed in writing by at least three members

SEC 2 The Secretary shall give all members due notice of proposed amendments

SEC 3 A four-fifths vote of the members present shall be required for the adoption of an amendment

ARTICLE X—Journal

SECTION 1 The official publication of the Society shall be the Journal of Pharmacology and Experimental Therapeutics

SEC 2 The Society shall elect an Editor-in-Chief for a term of three years and he with the approval of the Council shall appoint an Editorial Board of six members for a term of three years

SEC 3 The Editorial Board shall have direct authority and responsibility for the active editorial conduct of the Journal of Pharmacology and Experimental Therapeutics and shall have discretionary power in arranging details as to the conduct of the Journal

BY-LAWS

1 Papers to be read shall be submitted by the members of the Society to the Secretary, who, with

the President, shall be empowered to arrange the program. No person may orally present more than one paper. In case of joint authorship, the name of the individual who will orally present the paper shall stand first. Papers not read shall appear on the program as read by title.

2 An abstract of a paper to be read before the Society shall be sent to the Secretary with the

title. As early as possible after each meeting, the Secretary shall edit and publish the Proceedings of the Society together with abstracts in a publication authorized by the Society.

3 All applications for membership shall be accompanied by a copy of as many reprints as possible of the published work of the applicant.

THE AMERICAN SOCIETY FOR EXPERIMENTAL PATHOLOGY

Founded December 29, 1913

OFFICERS ELECTED 1916

President—PAUL R. CANNON, University of Chicago, Chicago, Illinois

Vice-President—DOUGLAS H. SPRUNT, University of Tennessee, Memphis, Tenn.

Secretary-Treasurer—FRIEDA S. ROBSCHT-ROBBINS, University of Rochester School of Medicine, Rochester, N. Y.

Councilors—H. P. SMITH, College of Physicians and Surgeons, Columbia University, New York 32, N. Y., JOHN G. KIDD, Cornell University Medical College, New York, N. Y.

Representative in the Division of Medical Sciences of the National Research Council—(July 1, 1946–June 30, 1949) H. P. SMITH, College of Physicians and Surgeons, Columbia Univ., New York, N. Y.

Representatives on the Council of the American Association for the Advancement of Science—MALCOLM H. SOULE, Univ. of Michigan, E. B. KRUMBHAAR, University of Pennsylvania (terms until June 30, 1947).

Representative on the Council of the Union of American Biological Societies—H. P. SMITH, Columbia Univ., College of Physicians and Surgeons, New York, N. Y.

Representatives on the Eli Lilly Award Committee (Jointly with the Society of American Bacteriologists) — For nominations MORTON McCUTCHEON, Univ. of Pennsylvania For Award SHIELDS WARREN, Harvard University

Representative on the Committee for the Placement Service—DOUGLAS H. SPRUNT, Univ. of Tennessee Medical School, Memphis, Tenn.

Representative in the Division of Medical Sciences of the National Academy of Sciences—H. P. SMITH, Columbia Univ., College of Physicians and Surgeons, New York, N. Y.

PAST OFFICERS

1914 R. M. PEARCE, President, JOHN F. ANDERSON, Vice-President, G. H. WHIPPLE, Secretary-

Treasurer, HARVEY CUSHING, DAVID MARINE, Councilors. 1915 THORALD SMITH, President, G. H. WHIPPLE, Vice-President, PLYTON ROUS, Secretary-Treasurer, DAVID MARINE, R. M. PEARCE, Councilors. 1916 SIMON FINKNER, President, LEO LOEB, Vice-President, PLYTON ROUS, Secretary-Treasurer, DAVID MARINE, R. M. PEARCE, Councilors. 1917 LUDVIG HEKTOEN, President, LEO LOEB, Vice-President, HOWARD T. KARSNER, Secretary-Treasurer, PAUL A. LEWIS, L. G. ROWNTREE, Councilors. 1918 H. GIDEON WELLS, President, W. G. MACCALLUM—Vice-President, HOWARD T. KARSNER, Secretary-Treasurer, L. G. ROWNTREE, LUDVIG HEKTOEN, Councilors. 1919 W. G. MACCALLUM, President, WILLIAM H. PARK, Vice-President, HOWARD T. KARSNER, Secretary-Treasurer, LUDVIG HEKTOEN, E. L. OPIE, Councilors. 1920 WILLIAM H. PARK, President, F. G. NOVY, Vice-President, HOWARD T. KARSNER, Secretary-Treasurer, E. L. OPIE, WADE H. BROWN, Councilors. 1921 F. G. NOVY, President, HOWARD T. KARSNER, Vice-President, WADE H. BROWN, Secretary-Treasurer, PAUL A. LEWIS, A. R. DOCHEZ, Councilors. 1922 HOWARD T. KARSNER, President, EUGENE L. OPIE, Vice-President, WADE H. BROWN, Secretary-Treasurer, A. R. DOCHEZ, GEORGE H. WHIPPLE, Councilors. 1923 EUGENE L. OPIE, President, ALDRED S. WARTHIN, Vice-President, WADE H. BROWN, Secretary-Treasurer, GEORGE H. WHIPPLE, H. GIDEON WELLS, Councilors. 1924 ALDRED S. WARTHIN, President, GEORGE H. WHIPPLE, Vice-President, EDWARD B. KRUMBHAAR, Secretary-Treasurer, H. GIDEON WELLS, FREDERICK L. GATES, Councilors. 1925 GEORGE H. WHIPPLE, President, WADE H. BROWN, Vice-President, EDWARD B. KRUMBHAAR, Secretary-Treasurer, FREDERICK L. GATES, DAVID MARINE, Councilors. 1926 WADE H. BROWN, President, DAVID MARINE, Vice-President, EDWARD B. KRUMBHAAR, Secretary-Treasurer, FREDERICK L. GATES, WILLIAM F. PETERSEN, Councilors. 1927 DAVID MARINE,

President, EDWARD B KRUMBHAR, Vice President, CARL V WELLER, Secretary-Treasurer, WILLIAM F PETERSEN, FREDERICK L GATES, Councilors 1928 EDWARD B KRUMBHAR, President, WILLIAM F PETERSEN, Vice President, CARL V WELLER, Secretary-Treasurer, FREDERICK L GATES, SAMUEL R HAYTHORN, Councilors 1929 WILLIAM F PETERSEN, President, FREDERICK L GATES, Vice-President, CARL V WELLER, Secretary-Treasurer, SAMUEL R HAYTHORN, PEYTON ROUS, Councilors 1930 FREDERICK L GATES, President, SAMUEL R HAYTHORN, Vice President, C PHILLIP MILLER, Secretary-Treasurer, PEYTON ROUS, CARL V WELLER, Councilors 1931 SAMUEL R HAYTHORN, President, PEYTON ROUS, Vice-President, C PHILLIP MILLER, Secretary-Treasurer, CARL V WELLER, S BURT WOLBACH, Councilors 1932 PEYTON ROUS, President, CARL V WELLER, Vice-President, C PHILLIP MILLER, Secretary-Treasurer, S BURT WOLBACH, OSKAR KLOTZ, Councilors 1933 CARL V WELLER, President, S BURT WOLBACH, Vice President, C PHILLIP MILLER, Secretary-Treasurer, OSKAR KLOTZ, ALPHONSE R DOCHEZ, Councilors 1934 S BURT WOLBACH, President, OSKAR KLOTZ, Vice-President, SHIELDS WARREN, Secretary-Treasurer, C PHILLIP MILLER, ALPHONSE R DOCHEZ, Councilors 1935 OSKAR KLOTZ, President, ALPHONSE R DOCHEZ, Vice-President, SHIELDS WARREN, Secretary-Treasurer, MORTON McCUTCHEON, C PHILLIP MILLER, Councilors 1936 ALPHONSE R DOCHEZ, President, C PHILLIP MILLER, Vice-President, SHIELDS WARREN, Secretary-Treasurer, MORTON McCUTCHEON, ERNEST W GOODPASTURE, Councilors 1937 C PHILLIP MILLER, President, MORTON McCUTCHEON, Vice-President, PAUL R CANNON, Secretary-Treasurer, ERNEST W GOODPASTURE, SHIELDS WARREN, Councilors 1938 MORTON McCUTCHEON, President, ERNEST W GOODPASTURE, Vice-President, PAUL R CANNON, Secretary-Treasurer, SHIELDS WARREN, JESSE L BOLLMAN, Councilors 1939 ERNEST W GOODPASTURE, President, SHIELDS WARREN, Vice-President, PAUL R CANNON, Secretary-Treasurer, JESSE L BOLLMAN, BALDUIN LUCKÉ, Councilors 1940 SHIELDS WARREN, President, JESSE L BOLLMAN, Vice-President, H P SMITH, Secretary-Treasurer, BALDUIN LUCKÉ, PAUL R CANNON, Councilors 1941 JESSE L BOLLMAN, President, BALDUIN LUCKÉ, Vice President, H P SMITH, Secretary-Treasurer, PAUL R CANNON, DOUGLAS H SPRUNT, Councilors 1942, 1943, 1944, 1945 BALDUIN LUCKÉ, President, PAUL R CANNON, Vice-President, H P SMITH, Secretary Treasurer, DOUGLAS H SPRUNT, FRIEDA S ROBSCHT-ROBBINS, Councilors

CONSTITUTION

ARTICLE I—Name

The Society shall be named "THE AMERICAN SOCIETY FOR EXPERIMENTAL PATHOLOGY"

ARTICLE II—Object

The object of this Society is to bring the productive investigators in pathology, working essentially by experimental methods, in closer affiliation with the workers in the other fields of experimental medicine

ARTICLE III—Time and Place of Meeting

The Society shall meet at the same time and place as the Federation of American Societies for Experimental Biology, which comprises at present the American Physiological Society, the American Society of Biological Chemists, the American Society for Pharmacology and Experimental Therapeutics, the American Society for Experimental Pathology, the American Institute of Nutrition and the American Association of Immunologists

ARTICLE IV—Membership

SECTION 1 Any American investigator who, through the use of experimental methods, has, within three years prior to his candidacy, contributed meritorious work in pathology, is eligible to membership

SEC 2 It shall be the policy of the Society to restrict its membership to as small numbers as is compatible with the maintenance of an active existence

SEC 3 There shall be two classes of members active and honorary members

Active members Candidates for active membership shall be nominated at or before an annual meeting by two members of the Society The nominators shall present to the Secretary in writing evidence of the candidate's qualifications for membership Nominations approved by the Council shall be presented to the Society for election at the next annual meeting following nomination For election a favorable ballot by a majority of the members present is necessary

Honorary members These may be elected from the active list or from the group of distinguished investigators at home or abroad who have contributed to the knowledge of pathology by experimental study They shall be elected only by the unanimous vote of the members present at time of nomination

SEC 4 Active members shall pay such annual dues as are determined upon, from year to year, by the Council Honorary members shall pay no dues, are not eligible to office, and have no vote in the business affairs of the Society, but they shall have

all the privileges of the active members in the scientific proceedings

SEC 5 Upon failure of an active member to pay dues for two years, notice shall be given to the member by the Secretary. At the end of the third year, if dues are still unpaid, such failure constitutes forfeiture of membership.

SEC 6 A motion for expulsion of a member must be thoroughly investigated by the Council, at this investigation the accused shall be afforded a hearing or may be represented by a member. Expulsion can be accomplished only after a unanimous vote by the Council in favor of expulsion, sustained by a four-fifths vote of the members present at the meeting.

ARTICLE V — *Officers*

The management of the Society shall be vested in a Council of five members, consisting of a President, a Vice-President, a Secretary-Treasurer, and two other members who shall be nominated by the Council and elected by the Society. Officers are elected by a majority vote. Vacancies shall be filled by the Council for the unexpired term.

The President and Vice-President shall hold office for one year and are ineligible for re-election during the following year. The Secretary-Treasurer is eligible for re-election. Councilors shall hold office for two years and are elected on alternate years. At the first election one Councilor shall be elected for a short term of one year.

ARTICLE VI — *Quorum*

SECTION 1 Three constitute a quorum of the Council. The Council decides by a majority vote.

SEC 2 A quorum of the Society for transaction of business shall be one-fourth of the total membership. In all questions brought before the Society a majority vote of those present shall decide, except as elsewhere provided for.

ARTICLE VII — *Annual Meeting*

SECTION 1 Papers shall be limited to ten minutes. However, on motion and with unanimous

consent, the time may be prolonged by a period not exceeding five minutes. The Council may make provision for longer papers on suitable occasions.

SEC 2 The subjects of papers must be confined to experimental work in pathology. In doubtful cases a liberal interpretation by the President and Secretary may prevail. The Council may invite, however, presentations dealing with any subject which it considers of considerable interest to the Society.

ARTICLE VIII — *Change of Constitution*

A motion concerning a change of the Constitution must be presented to the Council in writing by three members, and must be communicated to the members by the Secretary at least four weeks before the annual meeting. At this meeting such a change may be established when accepted by a four-fifths vote of the members present.

BY-LAWS

1 There must be in each year at least one meeting of the Council, which shall take place not later than the evening before the annual meeting.

2 At the end of the first session of the annual meeting the Secretary shall read the report of the Council. This report shall include (1) names of persons recommended for membership, (2) nominations for offices, (3) matters of general interest. The Secretary shall exhibit in a conspicuous place the names of candidates for membership recommended by the Council, together with the evidence of the qualifications of the candidates.

3 The election of officers and of new members, changes in the Constitution, etc., shall be voted upon at the end of the first session.

4 Changes in the By-Laws may be determined by a majority vote of those present.

5 In the year that a new Secretary-Treasurer is elected the incoming Council Member elected that year, or another member of the Council, shall become Assistant Secretary-Treasurer for the duration of the term of the Secretary-Treasurer.

THE AMERICAN INSTITUTE OF NUTRITION

Founded April 11, 1933, Incorporated November 16, 1934

Member of Federation 1940

OFFICERS ELECTED 1946

President—ARTHUR H SMITH

Vice-President—R M BETHKE

Secretary—H E CARTER

Treasurer—E M NELSON

Councilors—C A ELVEHJEM, D W WOOLLEY, H J ALMQUIST

Nominating Committee—I McQUARRIE, Chairman, H GOSS, T S HAMILTON, H E LONGENECKER, E W McHENRY

PAST OFFICERS

1933 L B MENDEL, President, H C SHERMAN, Vice-President, J R MURLIN, Secretary-Treasurer, E F DuBois, M S ROSE, Councilors 1934 J R MURLIN, President, E F DuBois, Vice-President, ICIE G MACY, Secretary, W M BOOTHBY, Treasurer, A H SMITH, AGNES FAIRMORGAN, R M BETHKE, Councilors 1935 J R MURLIN, President, E F DuBois, Vice-President, ICIE G MACY, Secretary, G R COWGILL, Treasurer, A H SMITH, R M BETHKE, L A MAYNARD, Councilors 1936 E F DuBois, President, MARY SWARTZ ROSE, Vice-President, G R COWGILL, Treasurer, ICIE G MACY, Secretary, R M BETHKE, L A MAYNARD, C A ELVEHJEM, Councilors 1937 MARY S ROSE, President, E V MCCOLLUM, Vice-President, G R COWGILL, Treasurer, ICIE G MACY, Secretary, L A MAYNARD, C A ELVEHJEM, P E HOWE, Councilors 1938 E V MCCOLLUM, President, T M CARPENTER, Vice-President, G R COWGILL, Treasurer, L A MAYNARD, Secretary, C A ELVEHJEM, P E HOWE, HELEN S MITCHELL, Councilors 1939 H C SHERMAN, President, T M CARPENTER, Vice-President, G R COWGILL, Treasurer, L A MAYNARD, Secretary, P E HOWE, HELEN S MITCHELL, A H SMITH, Councilors 1940 THORNE M CARPENTER, President, A G HOGAN, Vice-President, L A MAYNARD, Secretary, W H SEBRELL, JR, Treasurer, HELEN S MITCHELL, ARTHUR H SMITH, LYDIA J ROBERTS, Councilors 1941 A G HOGAN, President, L A MAYNARD, Vice-President, ARTHUR H SMITH, Secretary, W H SEBRELL, JR, Treasurer, T H JUKES, LYDIA J ROBERTS, H B LEWIS, Councilors 1942 L A MAYNARD, President, H B LEWIS, Vice-President, ARTHUR H SMITH, Secretary, W H SEBRELL, JR, Treasurer, LYDIA J ROBERTS, GENEVIEVE STEARNS, T H JUKES, Councilors 1943 H B LEWIS, President, ICIE G MACY-HOOBLER, Vice-President, ARTHUR H SMITH, Secretary, LYDIA J ROBERTS, GENEVIEVE STEARNS, T H

JUKES, Councilors 1944 ICIE G MACY-HOOBLER, President, WM C ROSE, Vice-President, ARTHUR H SMITH, Secretary, E M NELSON, Treasurer, GENEVIEVE STEARNS, T H JUKES and C A ELVEHJEM, Councilors 1945 WM C ROSE, President, ARTHUR H SMITH, Vice-President, H E CARTER, Secretary, E M NELSON, Treasurer, T H JUKES, C A ELVEHJEM, D W WOOLLEY, Councilors

CONSTITUTION

1 The name of the proposed society is the "AMERICAN INSTITUTE OF NUTRITION"

2 The purposes of the society are to further the extension of the knowledge of nutrition and to facilitate personal contact between investigators in nutrition and closely related fields of interest

3 The management of the American Institute of Nutrition shall be vested in a council consisting of the President, Vice President, Secretary, Treasurer and three additional members

BY-LAWS

ARTICLE I—Membership

SECTION 1 *Eligibility for membership* Members Qualified investigators who have independently conducted and published meritorious original investigations in some phase of the chemistry or physiology of nutrition and who have shown a professional interest in nutrition for at least 5 years shall be eligible for membership in the Society

SEC 2 *Nomination* Nominations for membership shall be made and seconded by members of the Society on blanks furnished by the Secretary. Nominations shall be submitted to the Council who shall determine eligibility and make recommendation to the Society at a regular meeting

SEC 3 *Election to membership* A A nominee for membership may be voted for by ballot at any meeting of the Society after the Council has reported its findings on his eligibility B A majority of the ballots cast shall elect

SEC 4 *Forfeiture* If a majority of the Council after due notice to the member in question and opportunity for a hearing, shall decide that the interests of the Society require the expulsion of a member, the Secretary shall send a notice of this decision to each member at least two weeks before the next annual meeting At this meeting the Secretary shall, on behalf of the Council, propose the expulsion, and if two thirds of the members present vote for it, the member shall be expelled, his

assessment for the current year shall be returned to him, and he shall cease to be a member of the Society

ARTICLE II—*Meetings and Quorum*

SECTION 1 *Annual* The annual meeting of the Society shall be held on the date fixed by the Certificate of Incorporation

SEC 2 *Special* A special meeting may be called at any time by the President, or in case of his absence or disability, by the Vice-President, and must be called at the request in writing of a majority of the Council or fifty members of the Society Notice specifying the purpose of such meeting shall be mailed to each member at least ten days previous thereto The Council shall select the places at which meetings shall be held

SEC 3 *Quorum* Thirty members shall constitute a quorum at all meetings of the Society, but in the absence of a quorum any number shall be sufficient to adjourn to a fixed date

ARTICLE III—*Officials*

SECTION 1 *Officers* The officers shall be a President, and a Vice-President, who shall be elected annually, and a Secretary and Treasurer, each of whom shall be elected to serve for a term of three years These officers shall be elected by the members of the Society Their terms of office shall commence on July 1 of the year in which they are elected

SEC 2 *Council* The officers so selected and three additional members, one of whom shall be elected at each annual meeting to serve a term of three years, shall constitute a Board of Trustees and shall be known as 'The Council' (When this provision is first put into effect one member shall be elected for 1 year, one for 2 years and the third for 3 years)

SEC 3 *Duties of Officers* The powers and duties of the officers elected by the Society shall be such as usually devolve upon their respective positions

ARTICLE IV—*The Council*

SECTION 1 *Powers* The general management of the Society during the intervals between meetings shall be vested in the Council, which shall regularly perform the ordinary duties of an executive committee and possess all the powers conferred upon the Board of Trustees of an educational institution chartered by the Education Department of the University of the State of New York A permanent charter was issued to the American Institute of Nutrition under date of November 16, 1934

SEC 2 *Reports* The Council shall report to the Society its findings on the eligibility of candidates for membership, and on all charges of a violation of these By-Laws

ARTICLE V—*Nominating Committee*

SECTION 1 *Membership* A The Nominating Committee shall consist of five members appointed for the coming year by the retiring President Members who have served on the Nominating Committee for two consecutive years shall be ineligible for reappointment until after a lapse of one year B The President shall designate one member to be Chairman of the Nominating Committee

SEC 2 *Nomination of Officials* A The Nominating Committee shall make at least one nomination for each of the four offices, for each of the additional positions on the Council to be filled by vote of the members and for each of the positions on the Editorial Board to be vacated at the time of the annual meeting Any member of the Institute may submit nominations to the Nominating Committee for its consideration along with those nominations made by the members of the Nominating Committee B The nominations by the Nominating Committee shall be transmitted to the Secretary at least six weeks before the annual meeting at which they are to be considered C The Secretary shall send to every member, at least two weeks before the annual meeting, a printed ballot containing the list of nominees and space for such additional names as the member wishes to propose, and at the same time shall notify the members that they may vote by mail, returning to the Secretary the marked ballot in the envelope provided, at such a time and place as the Secretary may designate, or the ballot may be delivered to the Secretary at the beginning of the business session at which the elections are to take place

SEC 3 *Election of Officials* A At the beginning of the business session the Secretary shall present to the tellers, appointed by the President, the ballots submitted by the members and the ballots shall be counted forthwith B A majority of votes cast shall be necessary to elect an official

SEC 4 *Filling of Vacancies* A The Nominating Committee shall fill all vacancies in elective positions except such as may occur at a meeting of the Society B The President of the Society shall fill all vacancies in appointive positions

ARTICLE VI—*Financial*

SECTION 1 *Dues* The dues shall be the annual cost of subscription to The Journal of Nutrition for members plus an annual assessment which shall be determined by majority vote at the annual meetings, upon recommendation of the Council, and shall be due within a month after the annual meeting A member on attaining the age of 65 may elect to be relieved from all financial obligations to the Institute including subscription to the Journal of Nutrition

SEC 2 Expenditures No expenditures from the general funds of the Society except those required in the performance of the ordinary official duties shall be made except by vote of the Society or the Council

SEC 3 Penalty for non-payment of dues A Members in arrears for dues for two consecutive years shall forfeit their membership B Delinquent members may be reinstated by the Council provided all indebtedness to the Society is liquidated

ARTICLE VII—*The Journal of Nutrition*

SECTION 1 The American Institute of Nutrition designates The Journal of Nutrition as its official organ of publication

SEC 2 In accordance with the expressed wish of the Wistar Institute of Anatomy and Biology, owner and publisher of The Journal of Nutrition, the American Institute of Nutrition shall nominate members of the Editorial Board for its official organ A The editorial management of The Journal of Nutrition shall be vested in an Editorial Board consisting of an Editor and twelve Board Members B The Editor shall be chosen by the Editorial Board to serve a term of five years beginning July 1 of the year in which he is chosen, and shall be eligible for reelection The Editor shall have the power to designate one of the Board Members to serve as his assistant, and such an appointee shall be called Associate Editor C Three members of the Institute shall be nominated by the Nominating Committee for membership on the

Editorial Board each year to serve a term of four years, replacing three retiring members and taking office May 1 of the year in which they are elected In the event of a vacancy in the membership of the Editorial Board occurring through death or other reason, the Nominating Committee, for each such vacancy to be filled shall make an additional nomination In this event the nominees elected who receive the greatest number of votes shall serve the longest term of vacancies to be filled D Retiring members of the Editorial Board shall not be eligible for renomination until one year after their retirement

ARTICLE VIII—*Papers on Scientific Subjects*

SECTION 1 The Secretary shall be authorized to arrange programs for the scientific sessions at the annual meetings

ARTICLE IX—*Changes in Constitution and By-Laws*

SECTION 1 Proposed changes in the Constitution and By-Laws must be sent in writing to the Secretary at least one month before the date of the meeting at which they are to be considered, and must be signed by at least three members The Secretary shall send a printed copy of any proposed change to each member at least two weeks before the next meeting and shall notify all members that they may vote by proxy

SEC 2 If at this meeting two-thirds of the votes cast shall favor the proposed change, it shall be made

THE AMERICAN ASSOCIATION OF IMMUNOLOGISTS

Founded June 19, 1913, Member of Federation 1942

OFFICERS ELECTED 1946

President—MICHAEL HEIDELBERGER, College of Physicians and Surgeons, 630 West 168th Street, New York 32, N Y

Secretary—ARTHUR F COCA, Pearl River, N Y

Treasurer—ALFRED J WEIL, Pearl River, N Y

Council—J J BRONFENBRENNER, MICHAEL HEIDELBERGER, ALFRED WEIL, P R CANNON, K F MEYER, G P BERRY, L D FELTON, ARTHUR F COCA

PAST OFFICERS

Presidents—1913 GERALD B WEBB 1915 JAMES W JOBLING 1916 RICHARD WEIL 1917 JOHN A KOLMER 1918 WILLIAM H PARK 1919 HANS ZINSSER 1920 RUFUS I COLE 1921 FREDERICK P GAY 1922 GEORGE W MCCOY 1923 H

GIDEON WELLS 1924 FREDERICK G NOVY 1925 WILFRED H MANWARING 1926 LUDVIG HEKTOEN 1927 KARL LANDSTEINER 1928 EUGENE L OPIE 1929 OSWALD T AVERY 1930 STANHOPE BAYNE-JONES 1931 ALPHONSE R DOCHEZ 1932 AUGUSTUS B WADSWORTH 1933 THOMAS M RIVERS 1934 FRANCIS G BLAKE 1935 WARFIELD T LONGCOPE 1936 SANFORD B HOOKER 1937 CARL TENBROECK 1938 DONALD T FRASER 1939 GEORGE P BERRY 1940 PAUL R CANNON 1941 KARL F MEYER 1942-1945 JACQUES J BRONFENBRENNER

Vice-Presidents—1913-1915 GEORGE W ROSS 1915 GEORGE P SANBORN 1916 JOHN A KOLMER
Secretary—1913-1918 MARTIN J SYNOTT
Treasurer—1913-1918 WILLARD J STONE
Secretary Treasurer—1918-1945 ARTHUR F COCA

CONSTITUTION AND BY-LAWS

Adopted April 6, 1917

ARTICLE I

SECTION 1 This Association shall be called "The American Association of Immunologists"

SEC 2 The purpose of the Association shall be to study the problems of immunology and its application to clinical medicine

ARTICLE II

SECTION 1 The Association shall be governed by a Council of seven, which shall consist of the officers of the association and enough active members to make a total of seven members

SEC 2 The officers of the Association shall be a President, a Secretary, and a Treasurer, who shall be nominated annually by the Council, and elected by the Society to serve for one year. Nominations of officers may be made also by members of the Society

SEC 3 No councilor is eligible for re-election until after one year, except the Secretary and the Treasurer, who are eligible for re-election

SEC 4 If any councilor without good and sufficient reason fails to attend two consecutive meetings of the Council he shall be considered to have resigned

SEC 5 The same person shall not serve as President more than one year consecutively

SEC 6 It is the duty of the Council to conduct the business of the Association and to elect the new members. Should a vacancy occur in the Council otherwise than by the expiration of the term of service, the Council may elect a member to serve for the unexpired portion of the term

ARTICLE III

SECTION 1 Active Members Any one actively engaged in the systematic study of problems relating to immunology shall be eligible to active membership

ARTICLE IV

Candidates for membership shall be nominated by two active members of the Association who shall present in writing to the Council evidence of the fitness of the candidates to become members of the Association

ARTICLE V

If a majority of the Council shall decide that the interests of the Society require the expulsion of a member, the Secretary shall send a notice of this decision to each active member at least two weeks before the next annual meeting. At this meeting the Secretary shall, on behalf of the Council, propose the expulsion, and if two-thirds of the members present vote for it, the member shall be

expelled, his assessment for the current year shall be returned to him, and he shall cease to be a member of the Society

ARTICLE VI

SECTION 1 A quorum of the Council for the transaction of all business shall be three

SEC 2 Any number of members present at the time appointed for the annual meeting of the Association, shall constitute a quorum

BY-LAWS

1 A regular meeting of the Association shall be held annually at such time and place as the Council shall determine

2 Special meetings of the Association may be held at the discretion of the Council

3 These regular and special meetings shall be open to all members of the Association

4 A meeting of the Council shall be held shortly before each annual session of the Association

5 Hereafter each Councilor shall serve for a period of six years. Under this rule the service of one member and also that of the Secretary-Treasurer terminates at the meeting of 1936. At that meeting two members shall be elected to the Council, one of whom may serve as Secretary-Treasurer. Thereafter the period of service of these two members shall run concurrently, hence, two members must be elected to the Council every six years in order to maintain a membership of seven

6 Past Presidents are honorary members of the Council

7 The titles of all communications to be presented before the Association shall be approved by the Council

8 Failure of an active member to offer a paper at least once in three years shall be equivalent to resignation. If in its judgment there is sufficient reason the Council may, in individual cases, suspend this rule

9 The dues of the Association shall be fixed annually by the Council

10 Failure to pay dues for three successive years shall constitute annulment of membership

11 The constitution and by-laws may be amended by a two-thirds vote of the active members present at any regular meeting

12 No amendment shall be adopted at the meeting at which it is proposed

13 The Journal of Immunology, which is the property and official organ of this Association, shall be administered for the Association by an editorial staff to consist of an Editor-in-Chief and at least three Associate Editors, with the advice of a Board of Editors

14 The members of the editorial staff shall be elected or may be removed by a majority vote of the Council of the Association

ALPHABETICAL LIST OF ALL MEMBERS OF THE SIX SOCIETIES

The parenthesis following each listed name gives the Society affiliation and year of election

- (1) The American Physiological Society
- (2) The American Society of Biological Chemists
- (3) The American Society for Pharmacology and Experimental Therapeutics
- (4) The American Society for Experimental Pathology
- (5) The American Institute of Nutrition
- (6) The American Association of Immunologists

HONORARY MEMBERS

- Adrian, E D Dept of Physiology, Cambridge University, Cambridge, England (1, 1946)
- Barcroft, Sir Joseph Dept of Physiology, Cambridge University, Cambridge, England (1, 1946)
- Castaneda, M Ruiz, M D Investigaciones Medicas, Hospital General, Mexico, D F *Director, Department of Medical Research* (6, 1942)
- Chopra, R N, M A, M D, Sc D (Cantab), F R C P (London) P I E School of Tropical Medicine, Calcutta, India *Director, Professor of Pharmacology* (3, 1938)
- Dale, H H Medical Research Council, National Institute for Medical Research, Hampstead, London, N W 3, England *Director, National Institute for Medical Research* (3, 1926)
- Hektoen, Ludvig, M D 629 S Wood St, Chicago, Ill *President, Chicago Tumor Institute* (6, 1919)
- Hitchens, Arthur P, M D Medical School, University of Pennsylvania, Philadelphia *Professor of Public Health and Preventive Medicine, Lt Col, M C, U S A* (6, 1913)
- Houssay, Bernardo A, M D Viamonte 2790, Buenos Aires, Argentina *Director, and Professor of Physiology* (1, 1942)
- Huntoon, F M, M D Woodbridge, Conn (6, 1918)
- Krogh, August Juliane Mararuesvej 34, Copenhagen, Denmark (1, 1946)
- Lapicque, L Laboratory of Physiology, The Sorbonne, Paris, France (1, 1946)
- Loewi, Otto, M D New York University College of Medicine, 477 First Ave, New York City *Research Professor in Pharmacology* (3, 1941)
- McCoy, George Walter, M D Louisiana State University Medical School, New Orleans *Director, Department of Public Health* (6, 1916)
- Novy, Frederick G, M D, Sc D, LL D 721 Forest Ave, Ann Arbor, Mich *Dean Emeritus and Professor Emeritus of Bacteriology, Medical School, University of Michigan* (6, 1920)
- Orbeli, L A Academy of Sciences of the USSR, Moscow, USSR (1, 1946)

- Rosenau, Milton J, M D, A M Medical School, University of North Carolina, Chapel Hill *Director, School of Public Health, Professor of Epidemiology, School of Public Health* (6, 1918)
- Sherrington, Sir Charles S, O M, Sc D, M D, F R S "Brookside," Valley Road, Ipswich, England *Former Waynflete Professor of Physiology, Oxford University, Former President of the Royal Society* (1, 1904)
- Sordelli, A Institute of Bacteriology, Department of Public Health, Buenos Aires, Argentina *Director* (6, 1942)

MEMBERS

- Abels, Jules C, M D Memorial Hospital, 444 E 68th St, New York City *Assistant Attending Physician* (4, 1944)
- Abramson, David I, M D Mayo General Hospital, Galesburg, Ill *Capt M C* (1, 1937)
- Abramson, Harold A, M D 133 E 58th St, New York City *Assistant Professor of Physiology, College of Physicians and Surgeons, Columbia University* (1, 1930, 2, 1934)
- Abreu, Benedict E, M S, Ph D, Division of Pharmacology, Univ of California Medical School, San Francisco *Assistant Professor of Pharmacology* (3, 1941)
- Acheson, George H, M D Harvard Medical School, 25 Shattuck St, Boston, Mass *Associate in Pharmacology* (1, 1942, 3, 1945)
- Adams, Georgian, M A, D Sc United States Department of Agriculture, Washington 25, D C *Senior Experiment Station Administrator, Office of Experiment Stations* (5, 1946)
- Adams, Mildred, M A, Ph D Takamine Laboratory, Clifton, N J *Research Chemist* (2, 1934)
- Adams, R Charles, M D, C M, M S (Anesthesiology), Mayo Clinic, Rochester, Minn *Instructor in Anesthesia, Mayo Foundation, University of Minnesota Member of Mayo Clinic Staff, Section on Anesthesia* (3, 1942)
- Adams, W Lloyd, M D, Ph D, 134 Tamarack Rd, Stapleton 4, N Y U S Public Health Service, Staten Island, N Y (3, 1942)

- Adams, Wright R , B S , M D University of Chicago, Dept of Medicine, Chicago 37, Ill *Associate Professor of Medicine* (1, 1916)
- Addis, Thomas, M D , M R C P Lane Hospital, San Francisco, Calif *Professor of Medicine, Stanford University* (1, 1922)
- Addison, William H F , M D School of Medicine, University of Pennsylvania, Philadelphia *Professor of Histology and Embryology* (1, 1928)
- Ades, Harlow Whiting, Ph D Box 731, Emory University, Ga (1, 1945)
- Adler, Harry F , M S , Ph D ASN 7828 S Kingston Ave , Chicago 40, Ill (1, 1913)
- Adolph, Edward Frederick, Ph D School of Medicine and Dentistry, University of Rochester, Rochester, N Y *Associate Professor of Physiology* (1, 1921)
- Adolph, William H , Ph D Yenching University, Peiping, China (2, 1946, 5, 1934)
- Ahlquist, Raymond P , M S , Ph D Dept of Pharmacology, Univ of Georgia School of Medicine, Augusta *Assistant Professor of Pharmacology* (3, 1945)
- Albanese, Anthony A , Ph D G-7 Tower Lab , Children's Medical Service, Bellevue Hospital, New York, N Y *Assistant Professor of Pediatric Biochemistry, New York University College of Medicine* (2, 1944)
- Albritton, Errett C , M D George Washington University Medical School, 1339 H St , N W , Washington, D C *Professor of Physiology and Head of the Department of Physiology* (1, 1933)
- Alexander, Robert S , A B , M A , Ph D School of Medicine, Western Reserve Univ , 2109 Adelbert Road, Cleveland, Ohio *Instructor in Physiology* (1, 1946)
- Algire, Glenn H , M D National Cancer Institute, Bethesda, Md *Senior Assistant Surgeon, U S Public Health Service* (4, 1945)
- Allan, Frank N , M D Lahey Clinic, 605 Commonwealth Ave , Boston, Mass *Co-director of the Medical Department* (4, 1930)
- Allen, Charles Robert, Ph D University of Texas, School of Medicine, Galveston *Assistant Professor of Department of Anesthesiology* (1, 1943)
- Allen, Frederick M , M D 1031 Fifth Ave , New York City *Professor of Medicine, Poly-clinic Medical School and Hospital* (1, 1924, 4, prior to 1920)
- Allen, J Garrott, M D University of Chicago, University Clinics, Chicago, Ill *Instructor in Surgery* (1, 1943)
- Allen, Lane, M S , Ph D , M D University of Georgia School of Medicine, University Place, Augusta *Associate Professor of Anatomy* (1, 1939)
- Allen, Shannon C , Ph D 6944 Armour Drive, Oakland 11, Calif *Pharmacology Laboratory, Western Regional Research Laboratory, Albany 6, Calif* (1, 1915)
- Allen, Willard M , M D Washington University School of Medicine, 630 S Kingshighway Blvd , St Louis, Mo *Professor of Obstetrics and Gynecology* (1, 1934)
- Allen, William F , Ph D , D Sc University of Oregon Medical School, Portland *Professor of Anatomy* (1, 1929)
- Alles, Gordon A , M S , Ph D 770 S Arroyo Parkway, Pasadena, Calif *Lecturer in Pharmacology, University of California Medical School, San Francisco, and Research Associate in Biology, California Institute of Technology, Pasadena* (1, 1932, 3, 1941)
- Allison, James B , Ph D Bureau of Biological Research, Rutgers Univ , New Brunswick, New Jersey *Professor of Biochemistry, Scientific Director, Bureau of Biological Research* (2, 1946)
- Almquist, Herman J , Ph D F E Booth Co Laboratories, 1290 Powell St , Emeryville, Calif *Director of Research* (2, 1937, 5, 1937)
- Alvarez, Walter C , M D Mayo Clinic, Rochester, Minn *Professor of Medicine, Mayo Foundation* (1, 1917, 3, 1921)
- Alving, Alf Sven, M D Billings Hospital, University of Chicago, 950 E 59th St , Chicago, Ill *Associate Professor of Medicine* (1, 1939)
- Amberg, Samuel, M D , F A A P Mayo Clinic, Rochester, Minn *Associate in Pediatrics, Mayo Clinic, Associate Professor of Pediatrics, Mayo Foundation* (1, 1903, 2, 1906, 3, 1909)
- Amberson, William R , Ph D University of Maryland School of Medicine, Baltimore *Professor of Physiology* (1, 1924)
- Ambrose, Anthony M , M S , Ph D Western Regional Research Laboratory, 800 Buchanan St , Albany, Calif *Pharmacologist, U S Department of Agriculture, Bureau of Agricultural Chemistry and Engineering* (3, 1937)
- Amoss, Harold L , M D M S , Dr P H , Sc D 68 Deerfield Drive, Greenwich, Conn (4, 1922, 6, 1917)
- Andersch, Marie A , Ph D University Hospital, Baltimore, Md *Biochemist, University Hospital, Instructor in Medicine, University of Maryland* (2, 1940)
- Andersen, Dorothy H , M D Babies Hospital, Broadway and 167th St , New York City *Associate in Pathology, Columbia University* (4, 1935)
- Anderson, Evelyn M , M A , M D University of California Hospital, San Francisco *Assistant Professor of Medicine* (1, 1934)
- Anderson, Hamilton H , M S , M D Pharmacology Laboratory, Univ of California Medical

- School, San Francisco *Professor of Pharmacology* (3, 1931)
- Anderson, Oscar Daniel, Ph D Dept of Psychology, Adelphi College, Garden City, L I, N Y (1, 1939)
- Anderson, Rudolph J, Ph D Sterling Laboratory, Yale University, New Haven, Conn *Professor of Chemistry* (2, 1915)
- Anderson, W A D, M A, M D Marquette University School of Medicine, Milwaukee, Wis *Professor of Pathology and Bacteriology* (4, 1941)
- Anderson, William E, M A Eastern State Farmers' Exchange, Westbrook Farm, Rockville, Conn *Biochemist* (2, 1931, 5, 1933)
- Andervont, H B, Sc D National Cancer Institute, Bethesda, Md *Principal Biologist, U S Public Health Service* (4, 1939)
- Andrews, James C, Ph D University of North Carolina, Chapel Hill *Professor of Biological Chemistry and Nutrition* (2, 1925)
- Andrus, E Cowles, M D Johns Hopkins Hospital, Baltimore, Md *Assistant Visiting Physician, Associate Professor of Medicine, Johns Hopkins University* (1, 1925)
- Anfinson, Christian B, Jr, M S, Ph D Dept of Biological Chemistry, Harvard Medical School, 25 Shattuck St, Boston, Mass *Associate in Biological Chemistry* (2, 1946)
- Angerer, Clifford, Ph D Ohio State University, Columbus *Instructor in Physiology* (1, 1943)
- Angevine, D Murray, M D Univ of Wisconsin Medical School, Madison, Wis *Professor of Pathology* (4, 1940)
- Angier, Roswell Parker, Ph D Route 4, Box 686, Tucson, Arizona *Emeritus Professor of Psychology, Yale Univ* (1, 1906)
- Ansbacher, Stefan, M S, D Sc 26 East 6th St, Cincinnati 2, Ohio (2, 1939)
- Anson, Mortimer L, Ph D Continental Foods, Inc, Hoboken, N J *Director of Chemical Research* (2, 1937)
- Apperly, Frank L, M A, D Sc, M D, F R C P Medical College of Virginia, Richmond *Professor of Pathology* (4, 1936)
- Arkin, Aaron, M A, M D, Ph D Suite 2006, 25 E Washington St, Chicago, Ill *Rush Professor of Medicine, U of Ill Prof and Chairman, Dept of Medicine, Cook County Graduate School* (1, 1914, 3, 1919)
- Armstrong Philip B, M D College of Medicine, Syracuse Univ, Syracuse 10, N Y *Professor of Anatomy* (1, 1945)
- Armstrong, W D, M S, M D, Ph D Medical Sciences Bldg, University of Minnesota, Minneapolis *Professor of Physiological Chemistry* (2, 1938)
- Arnold, Lloyd, A M, M D 1538 E 57th St, Chicago, Ill (4, 1930, 6, 1925)
- Arnow, L Earle, Ph D, M D Medical Research Division, Sharp and Dohme, Glenolden, Pa *Director of Research* (2, 1940)
- Aronson, Joseph D, M D Phipps Institute, University of Pennsylvania, Philadelphia 4 *Associate Professor of Bacteriology* (4, 1927, 6, 1925)
- Artom, Camillo, M D Bowman Gray School of Medicine, Winston Salem, N C *Professor of Biochemistry* (2, 1944)
- Ascham, Leah, Ph D Kansas State College, Manhattan *Professor, School of Home Economics* (5, 1935)
- Asenjo, Conrado F, Ch E, M S, Ph D Dept of Chemistry, School of Tropical Medicine, San Juan, Puerto Rico *Associate Professor of Chemistry, School of Tropical Medicine of the University of Puerto Rico under the Auspices of Columbia University* (2, 1944)
- Ashby, Winifred M, Ph D 305 10th St, N E, Washington, D C *Senior Scientist, Federal Security Agency (St Elizabeth's Hospital)* (6, 1923)
- Ashman, Richard, M S, Ph D School of Medicine, Louisiana State University, New Orleans *Professor of Physiology* (1, 1925)
- Astwood, Edwin Bennet, M D, C M, Ph D Pratt Diagnostic Hospital, 30 Bennet St, Boston, Mass *Research Professor of Medicine at Tufts Medical School* (1, 1939)
- Atkin, Lawrence, Ph D Wallerstein Labs, 180 Madison Ave, New York 16, N Y *Research Chemist* (2, 1946, 5, 1946)
- Aub, Joseph C, M D Harvard Medical School, Boston 15, Mass *Professor of Research Medicine* (1, 1919, 5, 1933)
- Auer, John, M D 1402 S Grand Blvd, St Louis, Mo *Professor of Pharmacology and Director of the Department, St Louis University School of Medicine* (1, 1905, 3, 1908)
- Austin, J Harold, M D 711 Maloney Clinic, 36th and Spruce Sts, Philadelphia, Pa *Director, Pepper Laboratory* (2, 1922)
- Austin, Richard Sisson, M D Cincinnati General Hospital, University of Cincinnati, Cincinnati, O *Professor of Pathology* (4, 1927)
- Avery, O T, M D, Sc D, LL D Hospital of the Rockefeller Institute, 66th St and York Ave, New York City *Member Emeritus, Rockefeller Institute for Medical Research* (4, 1921, 6, 1920)
- Axtmayer, Joseph H, B S, A M, Ph D University of Puerto Rico, Rio Piedras, Puerto Rico *Professor of Chemistry* (5, 1935)
- Ayo, Corrado, M D, 1st Lt M C Veteran's Adm Hospital, Unit 1, General Delivery, Hines, Ill (6, 1944)
- Babkin, B P, M D, D Sc, F R S C McGill University, Montreal, Canada *Professor of Physiology* (1, 1924)

- Bachem, Albert, Ph D College of Medicine, University of Illinois, 1853 W Polk St, Chicago *Professor of Biophysics* (1, 1933)
- Bachman, Carl, M D Mobile Hospital No 5, c/o Fleet P O, San Francisco, Calif *Lieut Commander* (2, 1941)
- Bachmann, George, M S, M D, F A C P 1088 Lullwater Road, N E, Atlanta, Ga *Professor of Physiology, Emory University School of Medicine* (1, 1912)
- Baer, Erich, Ph D Banting Institute, 100 College St, Toronto, Canada *Assistant Research Professor of Organic Chemistry, University of Toronto* (2, 1942)
- Baernstein, Harry D, M S, Ph D National Institute of Health, Bethesda, Md *Biochemist* (2, 1934)
- Baetjer, Anna M, D Sc Johns Hopkins School of Hygiene and Public Health, 615 N Wolfe St, Baltimore 5, Md *Assistant Professor of Physiological Hygiene* (1, 1929)
- Bahrs, Alice M, M A, Ph D The Martha Washington Hotel, 10th and Montgomery Sts, Portland, Ore (1, 1933)
- Bailey, Cameron Vernon, M D, C M 303 E 20th St, New York City *Clinical Professor of Medicine, New York Post-Graduate Medical School, Columbia University* (2, 1920, 5, 1933)
- Bailey, Orville T M D Harvard Univ Medical School, 25 Shattuck St, Boston, Mass *Assistant Professor in Pathology* (4, 1939)
- Bailey, Percival, M D, Ph D Univ of Illinois College of Medicine, 1853 West Polk St, Chicago 12, Ill *Professor of Neurology and Neurosurgery* (1, 1941)
- Baitsell, George Alfred, A M, Ph D Yale University, Osborn Zoological Laby, 165 Prospect St, New Haven, Conn *Professor of Biology* (1, 1915)
- Baker, A B, M D University of Minnesota Medical School, 19 Millard Hall, Minneapolis *Associate Professor of Neuropsychiatry and Neuropathology* (4, 1940)
- Baker, Roger D, M D Medical College of Alabama, Birmingham 5 *Professor of Pathology* (4, 1939)
- Baldes, Edward J, A M, Ph D Mayo Foundation, Rochester, Minn *Assistant Professor of Physics, Mayo Foundation, Graduate School, University of Minnesota* (1, 1930)
- Baldwin, Francis Marsh, A M, Ph D University of Southern California, Los Angeles *Professor of Zoology and Director of Experimental Marine Biology* (1, 1919)
- Bale, William F, Ph D University of Rochester, School of Medicine and Dentistry, Rochester, N Y *Associate in Radiology* (1, 1943)
- Ball, Eric G, M A, Ph D Harvard Medical School, Boston, Mass *Professor of Biochemistry* (2, 1934)
- Ball, Howard A, M D San Diego County General Hospital, N Front St, San Diego, Calif *Pathologist, San Diego County General and Paradise Valley Hospitals* (4, 1937)
- Balls, Arnold Kent, Ph D Enzyme Research Laboratory, U S Bureau of Agricultural and Industrial Chemistry, Western Regional Research Laboratory, 800 Buchanan St, Albany 6, Calif *Head Chemist, Adjunct Professor, The George Washington University (on leave)* (2, 1932)
- Banus, Mario Garcia, M Sc, D Sc Tufts College Medical School, Boston, Mass *Associate Professor of Physiology* (1, 1927)
- Bard, Philip, A M, Ph D Johns Hopkins University School of Medicine, 710 N Washington St, Baltimore, Md *Professor of Physiology, Member National Academy of Sciences* (1, 1929)
- Barker, H A, Ph D 3048 Life Science Bldg, Univ of California, Berkeley 1, Calif *Associate Professor of Soil Microbiology* (2, 1946)
- Barker, S B, Ph D College of Medicine, State University of Iowa, Iowa City *Associate Professor of Physiology* (1, 1938)
- Barlow, Orpheus W, M D, Ph D R F D 3 Warwick Road, Winchester, N H (1, 1936, 3, 1944)
- Barnes, B O, A M, Ph D Box 967, Station Hospital, KAVI, Kingman, Ariz *Professor of Health Education, University of Denver* (1, 1932)
- Barnes, LaVerne A, B S, M S, Ph D Naval Medical Research Institute, National Naval Medical Center, Bethesda 14, Maryland *Head, Bacteriology Facility* (6, 1931)
- Barnes, Richard Henry, Ph D Sharp & Dohme, Glenolden, Pa *Director of Biochemical Research, Medical Research Division* (2, 1941, 5, 1944)
- Barnes, Thomas C, D Sc Hahnemann Medical College, Philadelphia, Penna *Associate Professor of Physiology* (1, 1942)
- Barnum, Cyrus P, Jr, Ph D 210 Millard Hall, Univ of Minnesota, Minneapolis 14, Minn *Assistant Professor of Physiological Chemistry* (2, 1946)
- Barott, Herbert G, E E U S Department of Agriculture, National Agricultural Research Center, Beltsville, Md *Biophysicist, Animal Nutrition Division, Bureau of Animal Industry* (5, 1938)
- Barrera, S Eugene, M D Albany Medical College, New Scotland Ave, Albany, N Y (1, 1937)
- Barron, Donald H, M S, Ph D, M A (Cambridge) Yale University School of Medicine, New Haven, Conn *Associate Professor of Physiology* (1, 1943)
- Barron, E S Guzman, M D Dept of Medicine, Univ of Chicago, Chicago 37, Ill *Associate Professor of Biochemistry* (2, 1931)

- Bartley, S Howard, Ph D Dartmouth Eye Institute, Dartmouth College, Hanover, N H Assistant Professor of Research in Physiological Optics (1, 1935)
- Bass, Allan D, M S, M D Univ of Syracuse School of Medicine, Syracuse, N Y Professor of Pharmacology (3, 1944)
- Batchelder, Esther L, A M, Ph D Rhode Island State College, School of Agriculture and Home Economics, Kingston Head of Department of Home Economics (5, 1933)
- Briteman, John B, Ph D Mayo Aero Medical Unit, Mayo Clinic, Rochester, Minn Associate (1, 1945)
- Bates, Robert W, Ph D E R Squibb and Sons, Biological Laboratories, New Brunswick, N J Head, Endocrine Products Dept (2, 1936)
- Batterman, Robert C, M D New York University College of Medicine, 477 First Ave, New York City Instructor in Therapeutics (3, 1941)
- Baudisch, Oskar, Ph D Saratoga Springs, N Y Director of Research, Saratoga Springs Authority, State of New York (2, 1931)
- Bauer, J H, M D The Rockefeller Foundation, 20 Rue de la Baume, Paris, (8^e) France (4, 1935)
- Bauer, Walter, M D Massachusetts General Hospital, Boston Associate Professor and Tutor in Medicine, Harvard Medical School, Colonel, MC, Army Service Forces Hq 8th Service Command, Dallas, Texas (1, 1929)
- Bauman, Louis, M D Presbyterian Hospital, New York City Assistant Professor of Clinical Medicine, Columbia University (2, 1912)
- Baumann, Carl A, M S, Ph D Biochemistry Dept, University of Wisconsin, Madison Professor of Biochemistry (2, 1938, 5, 1938)
- Baumann, Emil J, Ph D 7 Church Lane, Scarsdale, N Y Chemist, Montefiore Hospital (2, 1922)
- Baumberger, J Percy, M S, Sc D Stanford University, Calif Professor of Physiology (1, 1921)
- Baxter, James G, Ph D 228 Sagamore Drive, Rochester 12, N Y Supervisor, Organic Research Dept, Distillation Products, Inc (2, 1946)
- Bayne-Jones, Stanhope, M D Yale University, School of Medicine, New Haven, Conn Professor of Bacteriology (4, 1927, 6, 1917)
- Bazett, Henry C, M A, M D, F R C S University of Pennsylvania, School of Medicine, Philadelphia Professor of Physiology (1, 1921)
- Beach, Eliot F, Ph D 660 Frederick St, Detroit 2, Mich Assistant Director, Research Laboratory, Children's Fund of Michigan (2, 1941, 5, 1942)
- Benn, John W, M S, Ph D, M D University of Michigan, Ann Arbor Professor of Physiology (1, 1932)
- Beard, Howard H, M A, Ph D Chicago Medical School, 710 S Wolcott Ave, Chicago, Ill Professor of Biological Chemistry (2, 1928, 5, 1933)
- Beard, Joseph W, M D Duke Hospital, Durham, N C Associate Professor of Surgery (4, 1938, 6, 1940)
- Beazell, James Myler, Ph D, M D 104 South Michigan Ave, Chicago, Ill Instructor in Physiology and Pharmacology, Northwestern Univ School of Medicine (1, 1939)
- Beck, Claude S, M D Lakeside Hospital, Cleveland, O Professor of Neurosurgery, Western Reserve University, Associate Surgeon, Lakeside Hospital (4, 1930)
- Beck, Lyle V, M S, Ph D Hahnemann Medical College, 235 N 15th St, Philadelphia, Pa Associate Professor of Physiology (1, 1941)
- Becker, R Frederick, M S, Ph D Dept of Anatomy, Univ of Washington, Seattle 5, Wash (1, 1941)
- Becker, Theodore J, M A, Ph D Sterling-Winthrop Research Institute, 33 Riverside Avenue, Rensselaer, N Y Head, Pharmacology Section (3, 1944)
- Beckman, Harry, M D Marquette University School of Medicine, Milwaukee, Wis Professor and Director of the Department of Pharmacology (3, 1937)
- Beecher, Henry K, M D Massachusetts General Hospital, Boston Dorr Professor of Research in Anaesthesia, Harvard Medical School, Anesthetist-in-Chief, Massachusetts General Hospital (3, 1940)
- Behnke, Albert R, M S, M D Naval Medical Research Institute, Bethesda, Md Executive Director (1, 1946)
- Behre, Jeanette Allen, Ph D Department of Biochemistry, College of Physicians and Surgeons, 630 W 168th St, New York City Associate (2, 1925)
- Belding, David L, M D Boston University School of Medicine, Boston, Mass Professor of Bacteriology and Experimental Pathology (4, 1927)
- Belding, Harwood S, Ph D Fatigue Laboratory, Harvard University, Soldier's Field, Boston, Mass Assistant Professor of Industrial Physiology (1, 1945)
- Bell, E T, M D 110 Anatomy Bldg, University of Minnesota, Minneapolis Professor of Pathology (4, 1931)
- Benedict, Francis Gano, Ph D, Sc D, M D

- Machiasport, Mc *Member of the National Academy of Sciences* (1, 1904, 2, 1906)
- Benham, Olive Ray**, B S Connecticut State Department of Health, Bureau of Laboratories, Hartford *Chief Serologist* (6, 1914)
- Bennett, A Lawrence**, Ph D, M D College of Medicine, University of Nebraska, Omaha *Professor of Physiology and Pharmacology* (1, 1941)
- Bennett, Granville A**, M D University of Illinois College of Medicine, 1853 West Polk Street, Chicago *Professor of Pathology* (4, 1931)
- Bennett, Henry S**, M D Mass Institute of Technology, Cambridge 30, Mass *Assistant Professor of Cytology* (1, 1946)
- Bennett, Leslie L**, M D University of California, Berkeley 4 *Assistant Professor of Physiology* (1, 1945)
- Bennett, Mary Adelia**, M A, Ph D Lankenau Hospital Research Institute, Philadelphia, Pa *Research Biochemist* (2, 1941)
- Benson, Clara C**, Ph D 160 Dorset St, West, Port Hope, Ontario, Canada *Professor Emeritus of Food Chemistry, University of Toronto* (2, 1906)
- Berg, Benjamin N**, M D 630 W 168th St, New York City *Associate in Pathology, Columbia University, College of Physicians and Surgeons* (4, 1928)
- Berg, Clarence P**, M A, Ph D Chemistry Department, State University of Iowa, Iowa City *Professor of Biochemistry* (2, 1933, 5, 1936)
- Berg, William N**, Ph D 225 W 106th St, New York City *Biochemist* (2, 1906)
- Bergeim, Olaf**, M S, Ph D 1853 W Polk St, Chicago, Ill *Associate Professor of Physiological Chemistry, University of Illinois College of Medicine* (1, 1916, 2, 1914)
- Bergmann, Werner**, Ph D Sterling Chemistry Building, Yale University, New Haven, Conn *Associate Professor* (2, 1934)
- Berkson, Joseph**, M A, M D, D Sc Mayo Clinic, Rochester, Minn (1, 1933)
- Bernheim, Frederick**, Ph D Box 3109, Duke Medical School, Durham, N C *Professor of Pharmacology* (2, 1933, 3, 1935)
- Bernthal, Theodore G**, M S, M D Dept of Physiology, Medical College, State of South Carolina, Charleston 16, S C *Professor of Physiology* (1, 1932)
- Berry, George Packer**, M D University of Rochester, Rochester, N Y *Assistant Dean, Professor of Bacteriology, Associate Professor of Medicine* (4, 1938, 6, 1934)
- Bessey, Otto A**, Ph D Public Health Research Institute of the City of New York, Inc, Foot of E 15th St, New York City *Member of the Institute, Chief of the Division of Nutrition and Physiology* (2, 1938, 5, 1943)
- Best, Charles Herbert**, C B E, M A, M D, D Sc (London), D Sc (Chicago), I R S I R P C(c), University of Toronto, Toronto, Ont, Canada *Director, Banting and Best Department of Medical Research and Department of Physiology* (1, 1923, 2, 1923)
- Bethell, Frank H**, M D 109 Lenawee Drive, Ann Arbor, Mich *Associate Professor of Internal Medicine and Assistant Director of the Thomas Henry Simpson Memorial Institute* (4, 1936)
- Bethke, Roland M**, M S, Ph D Ohio Agricultural Experiment Station, Wooster *In Charge of Nutritional Investigations* (2, 1928, 5, 1933)
- Beutner, R**, M D, Ph D 235 N 15th St, Philadelphia, Pa *Professor and Head of Department of Pharmacology, Hahnemann Medical College* (1, 1924, 3, 1924)
- Beyer, Karl H**, Ph D, M D Medical-Research Division, Sharp and Dohme, Inc, P O Box 7259, Glenolden, Pa *Director of Pharmacological Research* (1, 1912, 3, 1911)
- Bieter, Raymond N**, M D, Ph D University of Minnesota, Minneapolis *Professor of Pharmacology* (3, 1930)
- Bills, Charles E**, M A, Ph D Mead Johnson & Co, Evansville, Ind *Director of Research* (2, 1928, 5, 1935)
- Bing, Franklin C**, Ph D 1135 Fullerton Ave, Chicago, Ill *Director, American Institute of Baking, Assistant Professor of Physiology, Northwestern University Medical School* (2, 1931, 5, 1934)
- Bing, Richard J**, M D Johns Hopkins Hospital, Baltimore 5, Md *Assistant Professor of Surgery* (1, 1942)
- Binger, Carl A**, M D 125 E 73rd St, New York City *Assistant Professor of Clinical Medicine (Psychiatry), Cornell University Medical College* (1, 1927)
- Binkley, Stephen Bennett**, M S, Ph D Research Department, Parke, Davis & Co, Detroit, Mich (2, 1941)
- Bisbey, Bertha**, A M, Ph D Gwynn Hall, University of Missouri, Columbia *Professor of Home Economics* (5, 1933)
- Bischoff, Fritz E**, M S, Ph D Cottage Hospital, Santa Barbara, Calif *Director of Research* (2, 1928, 5, 1933)
- Bishop, George H**, Ph D Washington University Medical School, Euclid and Kingshighway, St Louis, Mo *Professor of Bio-Physics* (1, 1923)
- Biskind, Gerson R**, M D Mt Zion Hospital, San Francisco, Calif *Pathologist, Mt Zion Hospital, Clinical Instructor in Pathology,*

- University of California Medical School* (1, 1944)
- Black, Edgar C., Ph D Dept of Physiology, Dalhousie Univ., Halifax, Nova Scotia, Canada (1, 1943)
- Blair, Edgar A., M S, Ph D U S Army, General Section T I S, Fort Benning, Ga Lt Col (1, 1936)
- Blair, Henry A., M Sc, Ph D University of Rochester School of Medicine and Dentistry, Rochester, N Y Associate Professor of Physiology (1, 1934)
- Blake, Francis G., M D, M A (hon.), Sc D Yale University School of Medicine, New Haven, Conn Dean and Sterling Professor of Medicine (4, prior to 1920, 6, 1921)
- Blanchard Ernest W., Ph B, M S, Ph D Schieffelin and Co., 30 Cooper Sq., New York 3, N Y Director of Research (1, 1946)
- Blankenhorn, M A., M D University of Cincinnati, Cincinnati, O Professor of Medicine (4, 1932)
- Blatherwick, Norman R., M S, Ph D, Sc D Metropolitan Life Ins Co., 1 Madison Ave., New York City Director of Biochemical Laboratory (1, 1915, 2, 1915, 5, 1934)
- Blau, Nathan F., Ph D, Dept of Chemistry, University of Notre Dame, Notre Dame, Indiana Research Associate in Organic Chemistry (2, 1928)
- Blish, Morris J., M A, Ph D Amino Products Company, Rossford, O Research Director (2, 1944)
- Bliss, Chester Ittner, Ph D Conn Agr Expt Sta., P O Box 1106, New Haven Biometrician, Lecturer in Biometry, Yale University (3, 1944)
- Bliss, Eleanor A., Sc D Department of Preventive Medicine, Johns Hopkins Hospital, 615 N Wolfe St., Baltimore, Md Associate in Preventive Medicine, Johns Hopkins University, School of Medicine (6, 1931)
- Bloch, Konrad, Ph D Institute of Radiobiology and Biophysics, University of Chicago, Chicago, Illinois Assistant Professor of Biochemistry (2, 1944)
- Block, Richard J., Ph D 15 Cooper Rd., Scarsdale, N Y Director of Research, C M Armstrong Co., Associate, Department of Physiology and Biochemistry, New York Medical College, Flower and Fifth Avenue Hospital (2, 1934, 5, 1933)
- Block, Walter D., M S, Ph D University Hospital, Ann Arbor, Mich Assistant Professor of Biological Chemistry, Rackham Arthritis Research Unit (2, 1942)
- Bloom, William, M D 1419 E 56th St., Chicago, Ill Professor of Anatomy, University of Chicago (4, 1930)
- Bloomfield, A L., M D Stanford University Hospital, San Francisco, Calif Professor of Medicine (3, 1927, 4, 1927)
- Bloor, W R A M, Ph D, LL D School of Medicine and Dentistry, University of Rochester, Rochester, N Y Professor of Biochemistry (1, 1915, 2, 1910)
- Blum, Harold F., Ph D Naval Medical Research Institute, National Naval Medical Center, Bethesda, Md Principal Biophysicist (1, 1928)
- Blumberg, Harold, Sc D Sterling Winthrop Research Institute, 33 Riverside Ave., Rensselaer, N Y Senior Biochemist (5 1942)
- Blumenstock, Julius, M D S19 W Cornellia, Chicago, Ill (1, 1925)
- Blumgart, Herrmann L., M D Beth Israel Hospital, 330 Brookline Ave., Boston, Mass Associate Professor of Medicine, Harvard Medical School Lt Col M C (1, 1927)
- Blunt, Katharine, Ph D, LL D 38 Glenwood Ave., New London, Conn President Emeritus, Connecticut College for Women (2, 1921)
- Bock, Joseph C., Ch E, Ph D 2324 N 46th St., Milwaukee 10, Wis Professor Emeritus of Biochemistry, Marquette Univ Medical School, Biochemist, Milwaukee County Hospital (2, 1916)
- Bodansky, Aaron, Ph D Hospital for Joint Diseases, 1919 Madison Ave., New York City Biological Chemist (2, 1926)
- Bodansky, Oscar, Ph D, M D Department of Pharmacology, 1300 York Avenue, Cornell University Medical College, New York 21, N Y Research Associate in Pharmacology (2, 1937, 3, 1942)
- Bodine, Joseph Hall, Ph D State University of Iowa, Iowa City Professor and Head of Department of Zoology (1, 1925)
- Boell, Edgar J., Ph D Osborn Zoological Laboratory, Yale University, New Haven, Conn Associate Professor of Biology (1, 1942)
- Bogert, L Jean, Ph D Hotel Claremont, Berkeley, Calif (2, 1917)
- Bogert, Marston Taylor, Sc D, LL D, R N D Columbia University, New York 27, N Y Professor Emeritus of Organic Chemistry Member National Academy of Sciences (2, 1925)
- Bolliger, Adolph, Ph D Gordon Craig Research Laboratories, University of Sydney, Sydney, Australia Director of Research (2, 1928)
- Bollman, J L., M D Mayo Clinic, Rochester, Minn Associate in Division of Experimental Surgery and Pathology, Mayo Clinic, Professor of Physiology, Mayo Foundation, University of Minnesota (4, 1927)
- Bond, Glenn C., Ph D, M D The Upjohn Co.,

- Research Laboratories, Kalamazoo, Mich *Assistant Dept Head, Bacteriology Research* (6, 1939)
- Booker, Lela E**, Ph D General Mills, Inc, Minneapolis, Minn *Chief Nutritionist* (2, 1933, 5, 1933)
- Bookman, Samuel**, M A, Ph D 624 Madison Ave, New York City *Consulting Chemist, Mt Sinai Hospital* (2, 1912)
- Boor, Alden K**, M S, Ph D Department of Medicine, University of Chicago, Chicago, Ill *Research Associate (Associate Prof) of Biochemistry* (2, 1931)
- Boothby, W M**, M D, M A, F A C S, F A C P, Metabolism Laboratory, The Mayo Clinic, Rochester, Minn *Chief of Section of Clinical Metabolism in Division of Medicine, Mayo Clinic, Professor of Experimental Metabolism, Mayo Foundation, University of Minnesota* (1, 1915, 2, 1920, 3, 1923, 4, 1924)
- Bordley, James, III**, M D Johns Hopkins Hospital, Baltimore, Md *Associate Professor of Medicine, Johns Hopkins University* (1, 1938)
- Borsook, Henry**, M D, Ph D California Institute of Technology, Pasadena 4 *Professor of Biochemistry* (2, 1931)
- Bosworth, Alfred Willson**, A M, M D R D 4, Circleville, O *Consulting Chemist* (2, 1936, 5, 1935)
- Bott, Phyllis A**, M S, Ph D Woman's Medical College of Pennsylvania, East Falls, Philadelphia *Associate Professor of Physiological Chemistry* (2, 1938)
- Boucher, Robert V**, M A, Ph D 303 Frear Labs State College, Pa *Professor of Agricultural and Biological Chemistry* (5, 1945)
- Bouman, H D**, M D Northwestern Univ Med School, 303 E Chicago Ave, Chicago, Ill *Assistant Professor of Physical Medicine and Physiology* (1, 1943)
- Bourne, Wesley**, M D, C M, M Sc, F R C P, D A (R C P & S, Eng) McGill University, Montreal, Canada *Lecturer in Anesthetics, Dept of Pharmacology and Therapeutics* (3, 1936)
- Bourquin, Helen**, M S, Ph D 1331 N Tejon St, Colorado Springs, Colo (1, 1925)
- Bowman, Donald E**, A M, Ph D 6956 Warwick Rd, Indianapolis, Ind *Assistant Professor of Biochemistry, Indiana University School of Medicine* (2, 1944)
- Bowman, Katherine L**, B A 20 Plaza Street, Brooklyn 17, N Y (6, 1946)
- Boxer, George E**, Ph D 328 West 108th Street, New York 25, N Y *Senior Chemist, Research and Development Division, Dept of Biochemistry, Merck & Co* (2, 1946)
- Boyd, Eldon M**, M A, M D, C M Queen's University, Kingston, Ontario, Canada *Professor and Head of the Department of Pharmacology* (3, 1911)
- Boyd, T E**, Ph D 706 S Lincoln St, Chicago, Ill *Professor of Physiology, Loyola University, School of Medicine* (1, 1921)
- Boyd, William C**, A M, Ph D Boston University School of Medicine, 80 E Concord St, Boston, Mass *Associate Professor of Biochemistry* (2, 1910, 6, 1933)
- Boyden, Edward A**, A M, Ph D University of Minnesota, Minneapolis 11 *Professor of Anatomy and Chairman of the Department* (1, 1929)
- Boyer, Paul D**, M S, Ph D Division of Agric Biochem, University of Minnesota, St Paul *Assistant Professor* (2, 1911)
- Boyle, Paul E**, D M D School of Dentistry, University of Pennsylvania, 40th and Spruce Sts, Philadelphia 4 *Professor of Oral Pathology* (4, 1939)
- Bozler, Emil**, Ph D Ohio State University, Columbus *Associate Professor of Physiology* (1, 1932)
- Bradbury, James T**, M S, ScD Dept of Obstetrics and Gynecology, University Hospitals, Iowa City *Assistant Professor of Obstetrics and Gynecology* (1, 1941)
- Bradley, Harold C**, Ph D Memorial Institute Bldg, Madison, Wis *Professor of Physiological Chemistry, University of Wisconsin* (1, 1911, 2, 1908)
- Bradley, William B**, Ph D American Institute of Baking, 1135 Fullerton Ave, Chicago, Ill *Director of the Laboratories* (1, 1939)
- Branch, Charles F**, M D Children's Hospital, Boston, Mass *Director* (4, 1940)
- Branch, E Arnold G**, M D Bureau of Laboratories, General Hospital, St John, N B *Acting Director, Bureau of Laboratories, New Brunswick Department of Health* (4, 1929)
- Brand, Erwin**, Ph D 630 W 168th St, New York City *Associate Professor of Biological Chemistry, Columbia University* (2, 1929)
- Brandes, W W**, M D Roosevelt Hospital, W 59th St, New York City (4, 1931)
- Branham, Sara E**, Ph D, M D, ScD National Institute of Health, Bethesda, Md *Senior Bacteriologist* (6, 1926)
- Branion, Hugh Douglas**, M A, Ph D Ontario Agricultural College, Guelph, Canada *Professor and Head of Dept of Animal Nutrition* (5, 1933)
- Brassfield, Charles R**, Ph D University of Michigan, Ann Arbor *Associate Professor of Physiology* (1, 1937)
- Bratton, Andrew Calvin, Jr**, M A, Ph D Research Laboratories, Parke, Davis and Co,

- Detroit 32, Mich *Director of Pharmacological Research* (3, 1911)
- Braun, Herbert A, Ph D *Food & Drug Administration, Federal Security Agency, Washington, D C Associate Pharmacologist* (3, 1911)
- Brewer, George, M D *University of Pennsylvania, School of Medicine, Philadelphia Assistant Professor of Physiology* (1, 1937)
- Bridge, Edward M, M D 219 Bryant St, Buffalo, N Y *Research Professor, Department of Pediatrics, Univ of Buffalo* (2, 1940)
- Briggs, A P, M D *University of Georgia, Augusta Associate Professor in Biochemistry and Medicine* (2, 1923)
- Briggs, David, R, M S, Ph D *Division of Agricultural Biochemistry, University Farm, University of Minnesota, St Paul S, Minn Professor of Agricultural Biochemistry, Chemist, Minn Agriculture Experiment Station* (2, 1946)
- Brink, Frank, Jr, Ph D *Johnson Research Foundation, University of Pennsylvania, Philadelphia Fellow in Medical Physics, Johnson Research Foundation, Lecturer in Biophysics, Graduate School, University of Pennsylvania* (1, 1942)
- Brinkhaus, K M, M D *Dept of Pathology, School of Medicine, Chapel Hill, N C Associate Professor of Pathology* (4, 1939)
- Britton, Sydney W, M D *University of Virginia School of Medicine, University Professor of Physiology* (1, 1925)
- Brobeck, John R, M D, Ph D *Yale University School of Medicine, New Haven, Conn Instructor, Laboratory of Physiology* (1, 1943)
- Brodie, Bernard B, Ph D *New York University Research Service, Goldwater Memorial Hospital, New York City Research Associate in Biochemistry, Assistant Professor of Pharmacology, New York University Medical College* (2, 1940, 3, 1945)
- Brody, Samuel, M A, Ph D *Dairy Building, University of Missouri, Columbia Professor of Dairy Husbandry, College of Agriculture and Agricultural Experimentation* (2, 1929, 5, 1933)
- Bronfenbrenner, J J, Ph D, D P H *Washington University School of Medicine, St Louis, Mo Professor of Bacteriology and Immunology* (4, 1940, 6, 1918)
- Bronk, Detlev W, M S, Ph D, Sc D *The Elbridge Reeves Johnson Foundation for Medical Physics, University of Pennsylvania, Philadelphia Johnson Professor of Biophysics and Director, Johnson Foundation, Member National Academy of Sciences* (1, 1927)
- Brookes, Margaret C Hessler, A M, Ph D *University of Chicago, Chicago, Ill Assistant Professor, Department of Home Economics* (5, 1935)
- Brookhart, John M, B A, M S, Ph D 1940 W Eddy St, Chicago 13, Illinois *Assistant Professor, Physiology, Loyola Univ* (1, 1946)
- Brooks, Chandler McCuskey, M A, Ph D *Johns Hopkins University School of Medicine, Baltimore, Md Associate Professor of Physiology* (1, 1934)
- Brooks Clyde, Ph D, M D, LL D 139 East 36th St, New York 16, N Y *Professor of Physiology and Pharmacology, Lssex College of Medicine and Surgery* (1, 1910, 3 1912)
- Brooks, Matilda Moldenhauer, M S, Ph D *Department of Zoology, University of California, Berkeley Research Associate in Biology* (1, 1923)
- Brooks, Sumner Cushing, Ph D *University of California, Berkeley Professor of Zoology* (1, 1923)
- Brown, Goronwy Owen, M D 1325 S Grand Blvd, St Louis, Mo *Professor of Internal Medicine, St Louis University* (4, 1927)
- Brown, Claude P, M D *Penn State Board of Health, Bureau of Laboratories, 34th and Locusts Sts, Philadelphia, Pa, Director* (6, 1913)
- Brown, Dugald E S, M A, Ph D *New York University College of Dentistry, 209 E 23rd St, New York City Professor of Physiology* (1, 1932)
- Brown, Edgar D, Pharm D, M D *Paynesville, Minn Associate Professor of Pharmacology Emeritus* (1, 1907, 3, 1909)
- Brown, Ethan Allan, L R C P (Eng), A R C S (London), 75 Bay State Rd, Boston, Mass *Lecturer in Medicine, Tufts College Medical School, Physician in chief, Allergy Clinic, Boston Dispensary* (6, 1946)
- Brown, Frank A, Jr, M A, Ph D *Zoological Laboratories, Northwestern University, Evanston, Ill Associate Professor of Zoology* (1, 1940)
- Brown, John B, M S, Ph D *Ohio State University, Columbus Professor of Physiological Chemistry* (2, 1927, 5, 1934)
- Brown, R A, M S, Ph D, *The Research Laboratories, Parke Davis and Co, Detroit 32, Mich Head, Division of Nutritional Research* (5, 1946)
- Brown, Rachel, M S, Ph D 26 Buckingham Drive, Albany, N Y *Senior Biochemist, Division of Laboratories and Research, New York State Department of Health* (6, 1933)
- Brown, Robert V, Ph D *University of North Dakota, Grand Forks Professor of Physiology and Pharmacology* (1, 1945)
- Browne, J S L, M D, Ph D, F R S C *University Clinic, Royal Victoria Hospital, Montreal, Canada Assistant Professor of Medicine, McGill University* (1, 1934)

- Brownell, Katharine A**, M A, Ph D Department of Physiology, Ohio State University, Columbus Research Associate (1, 1943)
- Brues, Austin M**, M D Assistant Professor of Medicine, Harvard Medical School, Assistant Physician, Mass General Hospital (1, 1940)
- Bruger, Maurice**, M D, C M, M Sc 15 Gramercy Park N, New York, N Y Associate Clinical Professor of Medicine, New York Post-Graduate Medical School of Columbia University, Chief, Division of Pathological Chemistry, New York Post-Graduate Hospital (2, 1935, 5, 1935)
- Bruhn, John M**, Ph D Department of Physiology, Medical College of Alabama, 620 South 20th St, Birmingham 5 Professor of Physiology and Pharmacology (1, 1939)
- Bruner, Harry Davis**, M S, M D, Ph D University of Pennsylvania School of Medicine, Philadelphia 4 Associate in Pharmacology (3, 1945)
- Brunschwig, Alexander**, M D University of Chicago, Chicago, Ill Professor of Surgery (4, 1937)
- Bryan, W Ray**, Ph D Glen Rd, Rockville, Md Senior Biologist National Cancer Institute (1, 1934, 4, 1940)
- Buchanan, J William**, Ph D Northwestern University, Evanston, Ill Professor of Zoology (1, 1927)
- Buchbinder, Leon**, Ph D Department of Health, 125 Worth St, New York City (6, 1934)
- Buchbinder, William C**, M S, M D 104 S Michigan Ave, Chicago, Ill Assistant Professor of Medicine, Northwestern University Medical School, Associate in Medicine, Michael Reese Hospital (1, 1940)
- Bucher, Gladys R**, M S, Ph D, Dept of Physiology, Women's Medical College of Penn, Philadelphia, Pa Associate in Physiology (1, 1946)
- Buckner, G Davis**, Ph D Kentucky Agricultural Experiment Station, Lexington In Charge of Animal Nutrition (2, 1920)
- Bucy, Paul C**, M S, M D 25 E Washington St, Chicago, Ill Professor of Neurology and Neurological Surgery, University of Illinois (1, 1933)
- Buddingh, G John**, M D Vanderbilt University School of Medicine, Nashville, Tenn Professor of Bacteriology (4, 1940)
- Bueding, Ernest**, M D Dept of Pharmacology, Western Reserve Univ School of Medicine, Cleveland, Ohio Assistant Professor (2, 1946)
- Buell, Mary V**, Ph D 115 Ely Place, Madison 5, Wis (2, 1921)
- Bugbee, Edwin P**, M D 131 N Norwinden St, Springfield, Pa (1, 1928)
- Bugher, John C**, M D Rockefeller Foundation, 49 W 49th St, New York 20 Member of Staff International Health Division of the Rockefeller Foundation (4, 1935)
- Bukantz, Samuel C**, M D Washington University School of Medicine St Louis 10, Mo Research Assistant in Medicine (6, 1913)
- Bulatao, Emilio**, M D University of the Philippines, Manila, P I Professor of Physiology (1, 1921)
- Bulger, Harold A**, Ph D, M D Barnes Hospital, 600 S Kingshighway, St Louis, Mo Assistant Professor of Clinical Medicine, Washington University (5, 1933)
- Bull, Henry B**, Ph D Northwestern University Medical School, 303 E Chicago Ave, Chicago, Ill Associate Professor, Department of Chemistry (2, 1937)
- Bunde, Carl A**, M A, Ph D Southwestern Medical Foundation, Dallas, Texas Associate Professor of Physiology and Pharmacology (1, 1943)
- Bunney, William Edward**, Ph D F. R. Squibb and Sons, New Brunswick, N J Vice-President—Director of Manufacturing Labs (6, 1931)
- Bunting, Charles H**, M D 139 Armory St, Hamden, Conn Emeritus Professor of Pathology, University of Wisconsin, Lecturer in Pathology, Yale Medical School (4, 1913)
- Bunzell, H H**, Ph D Box 44, General Post Office, New York 1, N Y Director, Bunzell Laboratories (2, 1908)
- Burchell, Howard B**, M D, Ph D 799 3rd St, S W, Rochester, Minn Instructor in Medicine, Mayo Foundation, Graduate School, University of Minnesota, Consultant in Medicine, Mayo Clinic, Rochester, Minn (1, 1942)
- Burdick, H O**, M A, Sc D (hon) Alfred University, Alfred, N Y Professor of Biology (1, 1940)
- Burdon, Kenneth L**, Sc M, Ph D Baylor University College of Medicine, Houston, Texas Professor of Bacteriology, Consultant, United States Public Health Service (6, 1936)
- Burge, W E**, A M, Ph D University of Illinois, Urbana Associate Professor of Physiology (1, 1911)
- Burk, Dean**, Ph D National Cancer Institute, U S Public Health Service, Bethesda, Md Senior Chemist (2, 1939)
- Burky, Earl L**, M S, M D Johns Hopkins Hospital, Baltimore, Md Associate Professor of Ophthalmology, Wilmer Institute of Ophthalmology, Johns Hopkins University (6, 1931)
- Burns, Edward L**, M D Mercy Hospital, Toledo, Ohio Pathologist (4, 1939)
- Burr, George O**, M A, Ph D, LL D Experiment Station, H S P A, Honolulu, Hawaii, Head, Dept of Biochemistry & Physiology (2, 1928, 5, 1933)
- Burrill, Marie Wecker**, Ph D 402 Christopher Place, Louisville 8, Kentucky (1, 1944)

- Burris, Robert H, M S, Ph D Dept of Biochemistry, University of Wisconsin, Madison 6, Wis Assistant Professor of Biochemistry (2, 1946)
- Burrows Montrose T, M D 201 N El Molino Ave, Pasadena, Calif (4, prior to 1920)
- Burton, Alan C, Ph D Department of Medical Research, University of Western Ontario, London, Canada Assistant Professor of Medical Research (1, 1937)
- Burton-Opitz, Russell, M S, M D, Ph D 218 Bridle Way, Palisade, N J Attending Cardiologist, Lenox Hill Hospital, Attending Physician, Cumberland Hospital Consulting Cardiologist, Englewood, North Hudson, Holy Name and Hackensack Hospitals (1, 1902, 2, 1906, 3, 1919)
- Bush, Milton T, Ph D Vanderbilt University School of Medicine, Nashville, Tenn Research Associate in Pharmacology (3, 1938)
- Butler, Thomas C, M D Johns Hopkins School of Medicine, Dept of Pharmacology and Experimental Therapeutics, 710 N Washington St Baltimore 5, Md Associate Professor of Pharmacology and Experimental Therapeutics (3, 1938)
- Butt, Hugh R M D Mayo Clinic 102 Second Ave, S W Rochester, Minn Consultant in Medicine, Assistant Professor of Medicine, Mayo Foundation (5, 1942)
- Butts, Joseph S, M S, Ph D Oregon State College, Corvallis, Oregon Professor of Biological Chemistry (2, 1936, 5, 1936)
- Butz, Eleanor W J, Ph D Beltsville, Md Colaborator, Div Animal Husbandry, U S D A, Beltsville Research Center (6, 1935)
- Cahill, William M, Ph D 5532 Marlborough St, Detroit, Mich Consulting Biochemist (2, 1940)
- Cajori, Florian A, Ph D Dept of Biochemistry, Univ of Colorado Medical School, Denver 7, Colo Assistant Professor of Biochemistry (2, 1922, 5, 1933)
- Caldwell, Mary L, A M, Ph D Department of Chemistry, Columbia University, New York City Associate Professor of Chemistry (2, 1924, 5, 1933)
- Calloway, Nathaniel Oglesby Ph D, M D Medical School, University of Illinois, 1819 Polk St, Chicago 12 Assistant in Medicine (3, 1945)
- Calvin, D Bailey, M A, Ph D School of Medicine, University of Texas, Galveston Professor, Biological Chemistry, Dean, School of Medicine (1, 1934, 2, 1939)
- Cameron, A T, M A, D Sc, F I C, F R S C Medical College, Winnipeg, Manitoba, Canada Professor of Biochemistry, Faculty of Medicine, University of Manitoba, Biochemist, Winnipeg General Hospital (1, 1914, 2, 1914)
- Camp, Walter J R, M D, Ph D 1853 Polk St, Chicago, Ill Professor of Pharmacology and Therapeutics, University of Illinois (3, 1926)
- Campbell, Berry, Ph D University of Minnesota Minneapolis 11 Assistant Professor of Anatomy (1 1915)
- Campbell, Dan H, M S, Ph D Department of Chemistry, California Institute of Technology, Pasadena, Calif Assistant Professor of Immunochemistry (6, 1938)
- Campbell Louise H, Ph D 900 Windsor Ave, Windsor, Conn Retired (5, 1933)
- Campbell, James, M A, Ph D University of Toronto, Toronto, Ontario, Canada Assistant Professor of Physiology Lieutenant Commander, (S B) R C N V R (1, 1913)
- Campbell, Walter Ruggles, M A, M D, F R C P (C), F R S C 69 Madison Ave, Toronto, Canada Assistant Professor of Medicine and Clinical Medicine, University of Toronto, Assistant Physician, Toronto General Hospital (2, 1922)
- Cannan, R Keith, D Sc 477 First Ave, New York City Professor of Chemistry, New York University College of Medicine (2, 1931)
- Cannon, Paul R, M D, Ph D University of Chicago, Chicago, Ill Professor of Pathology (4, 1930, 6, 1929)
- Cantarow, Abraham, M D Jefferson Medical College, Philadelphia 7, Pa Professor of Physiological Chemistry (1, 1932, 3, 1935)
- Cantoni, G L, M D Long Island College of Medicine, 350 Henry St, Brooklyn 2, N Y Assistant Professor of Physiology and Pharmacology (3, 1945)
- Canzanelli, Attilio, M D Tufts College Medical School, 416 Huntington Ave, Boston, Mass Professor of Experimental Physiology (1, 1934)
- Carlson, A J, A M, Ph D, M D, LL D Hull Physiological Laboratory, University of Chicago, Chicago, Ill Professor of Physiology Emeritus, Member of the National Academy of Sciences (1, 1904, 5, 1933)
- Carlson, Loren D, Ph D Dept of Animal Biology, Univ of Washington, Seattle 5 (1, 1945)
- Carmichael, Emmett B, Ph D The Medical College of Alabama, Department of Biochemistry, Birmingham 5 Professor (1, 1931, 2, 1946)
- Carmichael, Leonard, Ph D, Sc D, Litt D, LL D Tufts College, Medford, Mass Director, the Tufts College Research Laboratory of Sensory Psychology and Physiology and President of the College (1, 1937)
- Carpenter, Thorne M, Ph D 27 Market St, Foxboro, Mass (1, 1915, 2, 1909, 5, 1935)

- Carr, C Jelleff, Ph D School of Medicine, University of Maryland, Baltimore *Associate Professor of Pharmacology* (3, 1940)
- Carr, Jesse L, M D University of California Medical School, Third and Parnassus Aves, San Francisco *Assistant Professor of Pathology* (4, 1940)
- Carter, Herbert E, M A, Ph D 452 Noyes Laboratory, Urbana, Ill *Professor of Biochemistry, University of Illinois* (2, 1937, 5, 1941)
- Cartland, George F, M S, Ph D The Upjohn Co, Research Dept, Kalamazoo, Mich *Head, Antibiotics Research* (2, 1936)
- Cary, Charles A, S B Dairy Research Laboratory, Beltsville, Md *Chief, Division of Nutrition and Physiology, Bureau of Dairy Industry, U S Department of Agriculture* (2, 1920)
- Casey, Albert Eugene, M D Baptist Hospital, Holy Name of Jesus Hospital, Gadsden, Ala *Pathologist, Director of Labs* (4, 1933)
- Cash, James Robert, M D University Hospital, Charlottesville, Va *Professor of Pathology, University of Virginia* (4, 1924)
- Castle, Edward S, M A, Ph D Biological Laboratories, Harvard University, Divinity Ave, Cambridge, Mass *Assistant Professor of General Physiology* (1, 1934)
- Castle, William B, M D, S M (Hon Yale), M D (Hon Utrecht) Boston City Hospital, Boston, Mass *Professor of Medicine, Harvard Medical School, Associate Director, Thorndike Memorial Laboratory and Director, II and IV Medical Services (Harvard), Boston City Hospital* (4, 1942)
- Catchpole, Hubert Ralph, Ph D 333 Cedar St, New Haven, Conn *Research Assistant in Physiology, (Assistant Professor), Yale University* (1, 1941)
- Cathcart, E P, M D, D Sc, LL D University of Glasgow, Glasgow, Scotland *Dean of University* (5, 1935)
- Catron, Lloyd, M D The City Hospital, Akron, O *Pathologist* (4, 1939)
- Cattell, McKeen, A M, Ph D, M D Cornell University Medical College, 1300 York Ave, New York City *Professor of Pharmacology* (1, 1928, 3, 1924)
- Cerecedo, Leopold R, Ph D Fordham University, New York City *Professor of Biochemistry* (2, 1931, 5, 1945)
- Chadwick, Leigh Edward, Ph D Medical Research Laboratory, Edgewood Arsenal, Md (1, 1944)
- Chaikoff, I L, A M, Ph D, M D University of California, Berkeley *Associate Professor of Physiology* (1, 1932)
- Chalkley, Harold W, A M, Ph D U S Public Health Service, National Institute of Health, Bethesda, Md *Senior Physiologist* (1, 1932)
- Chambers, Alfred H, Ph D University of Pennsylvania *Associate, Physiology* (1, 1916)
- Chambers, Leslie Addison, M S, Ph D Johnson Foundation for Medical Physics, University of Pennsylvania, Philadelphia *Lecturer in Biophysics, Associate in Medical Physics, Associate in Pediatrics* (1, 1910)
- Chambers, Robert, A M, Ph D New York University, Washington Square East, New York City *Research Professor of Biology* (1, 1932)
- Chambers, William H, M S, Ph D Cornell University Medical College, 1300 York Ave, New York City *Associate Professor of Physiology* (1, 1921, 5, 1933)
- Chandler, Caroline A, M D 615 N Wolfe St, Baltimore 5, Md *Assistant Professor of Preventive Medicine* (6, 1938)
- Chandler, Joseph P, M S, Ph D Cornell University Medical College, 1300 York Ave, New York City *Assistant Professor of Biochemistry* (2, 1944, 5, 1944)
- Chang, Min Cheuh, B Sc, Ph D Worcester Foundation, Shrewsbury, Mass *Associate Fellow* (1, 1946)
- Chanutin, Alfred, Ph D Box 1038 (University Station), Charlottesville, Va *Professor of Biochemistry, University of Virginia* (2, 1925)
- Chapman, C W, M Sc, Ph D University of Maryland, Baltimore *Professor of Pharmacology* (3, 1932)
- Chargaff, Erwin, Ph D Columbia University, College of Physicians and Surgeons, 630 W 168th St, New York City *Associate Professor of Biological Chemistry* (2, 1935)
- Charipper, Harry Adolph, M S, Ph D Washington Square College of Arts and Sciences, 100 Washington Square East, New York City *Professor of Biology and Chairman of the Department* (1, 1941)
- Chase, Aurin M, A M, Ph D Department of Biology, Princeton University, Princeton, N J. *Research Associate, Assistant Professor* (1, 1939)
- Chase, Harold F, B S, M D Western Reserve University School of Medicine, Cleveland, O *Assistant Professor of Pharmacology* (3, 1944)
- Chase, Merrill W, M S, Ph D Rockefeller Institute, 66th St and York Ave, New York City *Member of Staff* (6, 1938)
- Chasis, Herbert, M D, Med Sc D 44 E 67th St, New York City *Assistant Professor of Medicine, New York University, College of Medicine* (1, 1941)
- Chatfield, Charlotte, B S Production and Marketing Admin, Food Distribution Programs Branch, U S Dept of Agriculture, Washington 25, D C *Nutritionist* (5, 1941)

- Cheldelin, Vernon H, M S, Ph D Department of Chemistry, Oregon State College, Corvallis, Ore Associate Professor of Chemistry (5, 1946)
- Chen, Graham, Sc D, M D Dept of Pharmacology, University of Chicago, Chicago, Ill Research Associate (Assistant Prof) (3, 1944)
- Chen, K K, Ph D, M D The Lilly Research Laboratories, Indianapolis, Ind Director of Pharmacological Research, Professor of Pharmacology, Indiana University School of Medicine, Indianapolis (1, 1929, 3, 1942)
- Cheney, Ralph H M A, M S, Sc D Biology Dept Brooklyn College, Bedford Ave and Ave H, Brooklyn 10, N Y (3, 1934)
- Chenoweth, Maynard Burton, M D Dept of Pharmacology, Cornell Univ Med College 1300 York Ave, New York 21, N Y Assistant Professor of Pharmacology (3, 1945)
- Chesner, Alan M, M D The Johns Hopkins Hospital, Baltimore, Md Dean, Johns Hopkins Medical School, Associate Professor of Medicine (4, 1925)
- Child, Charles Manning, Ph D, D Sc (hon) Jordan Hall, Stanford University, Calif Member, National Academy of Sciences, Professor Emeritus, University of Chicago (1, 1923)
- Chow, Bacon F, Ph D Squibb Institute for Medical Research, New Brunswick, N J Head of Division of Protein Chemistry (2, 1940, 6, 1944)
- Christensen, L Royal, Ph D New York University College of Medicine, 477 First Ave, New York City Instructor in Bacteriology (6, 1942)
- Christian, Henry A, M D 20 Chapel St, Brookline, Mass Hersey Professor of the Theory and Practice of Physic, Emeritus, Harvard University Clinical Professor of Medicine, Tufts College Medical School, Physician in Chief, Emeritus, Peter Bent Brigham Hospital, Boston, Visiting Physician, Beth Israel Hospital, Boston (4, 1924)
- Christman, Adam A, Ph D University of Michigan Medical School, Ann Arbor Professor of Biological Chemistry (2, 1929)
- Chu, Wei-chang, M D Department of Pharmacology, Squibb Institute for Medical Research, New Brunswick, New Jersey (3, 1945)
- Clark, Ada R, M A, Ph D College of Physicians and Surgeons, 630 W 168th St, New York City Associate, Bacteriology, Teaching and Research (6, 1936)
- Clark, Byron B, M S, Ph D Albany Medical College, Albany, N Y Associate Professor of Physiology and Pharmacology (3, 1940)
- Clark, Eliot R, M D University of Pennsylvania, Philadelphia Professor and Head of Department of Anatomy (1, 1919)
- Clark, Ernest D, A M, Ph D 826 Skinner Bldg, Seattle 1, Wash Director of the Laboratories, Northwest Branch, National Cannery Association (2, 1912)
- Clark, George, Ph D Yerkes Laboratory of Primate Biology, Orange Park, Fla Assistant Professor of Psychobiology (1, 1943)
- Clark, Guy W, A M, Ph D c/o Lederle Laboratories, Inc, Pearl River, N Y Technical Director (2, 1922)
- Clark, Janet Howell, A M, Ph D Anderson Hall, University of Rochester, Rochester, N Y Dean of the College for Women and Professor in the Division of Biological Sciences (1, 1922)
- Clark, Paul F, Ph D University of Wisconsin Medical School, Madison Professor of Bacteriology (1, 1923, 6, 1928)
- Clark, William G, Ph D Department of Aviation Medicine, University of Southern California, Los Angeles 7 (1, 1942)
- Clark, William Mansfield, M A, Ph D, D Sc Johns Hopkins University, Baltimore, Md Professor of Physiological Chemistry, Member, National Academy of Sciences (2, 1920)
- Clarke, Hans Thacher, D Sc (London), F I C 630 W 168th St, New York City Professor of Biological Chemistry, Columbia University, College of Physicians and Surgeons (2, 1929)
- Clarke, Robert W 6 Audubon Court, Elizabethtown, Kentucky Physiologist, Armed Med Research Lab Fort Knox (1, 1936)
- Clausen, Samuel Wolcott, M D Strong Memorial Hospital, Rochester, N Y Professor of Pediatrics, School of Medicine, University of Rochester (2, 1922)
- Cleghorn, Robert Allen, M D, D Sc (Aberdeen) Department of Medicine, University of Toronto, Toronto, Ont, Canada Junior Demonstrator in Medicine, Junior Assistant Attending Physician, Toronto General Hospital (1, 1937)
- Climenko, David Robert, M D, Ph D Winthrop Chemical Co, 33 Riverside Ave, Rensselaer, N Y Pharmacologist, Associate in Biochemistry and Instructor in Medicine, Albany Medical College (1, 1933)
- Clowes, George Henry Alexander, Ph D, D Sc (hon), LL D (hon) Eli Lilly & Co, Indianapolis, Ind Director of Research (2, 1914, 6, 1919)
- Coca, Arthur F, A M, M D Pearl River, N Y Medical Director, Lederle Laboratories (6, 1916)
- Code, Charles F, Ph D, M D Mayo Foundation, Rochester, Minn Professor of Physiology (1, 1939)
- Coffey, Julia M, A B Division of Laboratories & Research, New York State Department of Health, Albany, N Y Associate Bacteriologist (6, 1937)
- Coghill, Robert D, M S, Ph D Abbott Labora-

- tonies, North Chicago, Illinois *Associate Director of Research* (2, 1932)
- Cohen, Barnett, M S, Ph D Johns Hopkins University School of Medicine, 710 N Washington St, Baltimore 5, Md *Associate Professor of Physiological Chemistry* (2, 1935)
- Cohen, Milton B, M D 10616 Euclid Ave, Cleveland, O *Director, The Asthma, Hay Fever and Allergy Foundation* (6, 1931)
- Cohen, Philip P, Ph D, M D Service Memorial Institute, University of Wisconsin, Madison *Associate Professor of Physiological Chemistry* (2, 1941)
- Cohen, Seymour S, Ph D Children's Hospital, 18th and Bainbridge, Philadelphia, Pa *Instructor, Univ of Pennsylvania Medical School* (2, 1946)
- Cohen, Sophia M, B S Division of Laboratories and Research, New York State Department of Health, Albany, N Y *Senior Bacteriologist* (6, 1938)
- Cohn, Alfred E, M D 300 Central Park W, New York City *Member, Rockefeller Institute for Medical Research* (1, 1911, 3, 1913)
- Cohn, Edwin J, Ph D, A M (Hon), Sc D (Hon) 183 Brattle St, Cambridge, Mass *Professor of Biological Chemistry, Harvard Medical School, Boston, Member, National Academy of Sciences* (1, 1919, 2, 1919)
- Cohn, Waldo E, M S, Ph D 109 Kingfisher Lane, Oak Ridge Tenn *Senior Biochemist, Clinton Laboratories, Knoxville, Tenn* (2, 1944)
- Cole, Arthur G, Ph D 1853 W Polk St, Chicago 12, Ill *Assistant Professor of Biological Chemistry, University of Illinois College of Medicine* (2, 1939)
- Cole, Harold N, Ph B, M D 1352 Hanna Bldg, Cleveland, O *Clinical Professor of Dermatology and Syphilology, Western Reserve University* (3, 1925)
- Cole, Kenneth S, Ph D 5618 Kimbark Ave, Chicago, Ill (1, 1934)
- Cole, Versa V, Ph D, M D Indiana University School of Medicine, 1040-1232 West Michigan St, Indianapolis *Assistant Professor of Pharmacology* (3, 1941)
- Collett, Mary Elizabeth, A M, Ph D Mather College, Western Reserve University, Cleveland, O *Associate Professor of Biology* (1, 1921)
- Collier, H Bruce, M A, Ph D Dept of Biochemistry, Univ of Saskatchewan, Saskatoon, Sask *Professor of Biochemistry* (2, 1944)
- Collings, William Doyné, Ph D University of Texas School of Medicine, Galveston *Assistant Professor of Physiology* (1, 1944)
- Collins, Dean A, M A, Ph D, M D Temple Univ School of Medicine, 3400 N Broad St, Philadelphia 10, Pa *Associate Professor of Physiology* (1, 1938)
- Collins, Russell J, A M, M D, F R C P (Can) M R C P (Edin) F A C P St John, New Brunswick, Canada *Medical Superintendent of St John Tuberculosis Hospital* (3, 1915)
- Collip, J B, A M, Ph D, D Sc, M D, C B E McGill University, Montreal, Quebec, Canada *Director, Research Institute of Endocrinology, and Professor of Biochemistry* (1, 1920, 2, 1920)
- Colowick Sidney P, Ph D The Public Health Research Inst of the City of New York, Inc, Foot of East 15th St, New York, N Y *Associate in the Division of Nutrition and Physiology* (2, 1941)
- Coman, Dale R, M D McManes Laboratory of Pathology, University of Pennsylvania School of Medicine, Philadelphia *Assistant Professor of Pathology* (4, 1939)
- Comroe, Julius H, Jr, M D University of Pennsylvania Medical School, Philadelphia *Professor of Physiology and Pharmacology* (1, 1943, 3, 1939)
- Conant, James B, Ph D 5 University Hall, Cambridge, Mass *President, Harvard University, Member, National Academy of Sciences* (2, 1932)
- Concepcion, Isabelo, M D College of Medicine and Surgery, Manila, P I *Professor of Physiology, University of the Philippines* (1, 1919)
- Conklin, Ruth E, M S, Ph D Vassar College, Poughkeepsie, N Y *Professor of Physiology* (1, 1940)
- Conn, Jerome W, M D University of Michigan Medical School, Ann Arbor, Mich *Associate Professor of Internal Medicine* (5, 1942)
- Conrad, Ralph M, Ph D Department of Chemistry, Kansas State College, Manhattan, Kansas *Associate Professor* (2, 1946)
- Cook, Donald Hunter, Ph D Department of Chemistry, University of Florida, Coral Gables 34 (2, 1929)
- Cooke, Robert A, A M, Sc D (hon), M D 60 E 58th St, New York City *Director, Department of Allergy, Roosevelt Hospital* (6, 1920)
- Coolidge, Thomas B, M D, Ph D Abbot Hall, University of Chicago, Chicago 37, Ill *Associate Professor of Biochemistry and Walter G. Zoller Memorial Dental Clinic* (2, 1942)
- Coon, Julius M, Ph D Dept of Pharmacology, Univ of Chicago, Chicago 37, Ill *Instructor in Pharmacology* (3, 1941)
- Coons, Callie Mae, Ph D Bureau of Human Nutrition and Home Economics, U S Dept of Agriculture, Washington, D C *Assistant Chief* (5, 1933)
- Cope, Otis M, M D New York Medical College, Flower and Fifth Avenue Hospitals, Fifth Ave

- at 106th St, New York City *Professor of Physiology and Biochemistry* (1, 1929)
- Copley, Alfred Lewin, M D *Laboratory of Cellular Physiology, Dept of Biology, New York Univ, Washington Square, New York 3, N Y Research Associate* (1, 1911)
- Corbin, Kendall B, M D 919 80th St, S W, Rochester Minn (1, 1911)
- Coreoran, Arthur Curtis, C M, M D *Cleveland Clinic Foundation, Cleveland 6, O* (1, 1910)
- Corey, Edward Lyman, Ph D *School of Medicine, University of Virginia, University Assistant Professor of Physiology* (1, 1931)
- Cori, Carl F, M D *Washington University School of Medicine, Kingshighway and Euclid Ave, St Louis, Mo Professor of Pharmacology and Biochemistry, Member, National Academy of Sciences* (2, 1925, 3, 1934)
- Cori, Gerty T, M D *Washington University School of Medicine, St Louis, Mo Research Associate Professor in Biochemistry* (2, 1927, 3, 1934)
- Corley, Ralph Conner, Ph D *Department of Chemistry, Purdue University, Lafayette, Ind Professor of Biochemistry* (2, 1927)
- Cornwall, Leon, M D 55 E 76th St, New York City *Attending Neurologist, N Y Neurological Institute* (6, 1920)
- Corper, Harry J, M D, Ph D 1295 Clermont St, Denver, Colo *Director of Research, National Jewish Hospital* (2, 1912)
- Corson, Samuel A, M S, Ph D *Department of Physiology, University of Minnesota School of Medicine, Minneapolis Research Associate* (1, 1943)
- Co Tui, Frank, M D *New York University College of Medicine, 477 First Ave, New York City Associate Professor of Experimental Surgery* (3, 1931)
- Cournand, André Frederic, M D *Chest Service, Bellevue Hospital, CD Building, 1st Ave at 28th St, New York City Assistant Professor of Medicine, College of Physicians and Surgeons, Columbia University* (1, 1944)
- Cowgill, George Raymond, Ph D 333 Cedar St, New Haven, Conn *Professor of Nutrition, Yale University* (1, 1923, 2, 1922, 5, 1933)
- Cox, Gerald J, M S, Ph D 200 S 7th Ave, LaGrange, Ill *Research Group Leader, Corn Products Refining Co* (2, 1930, 5, 1935)
- Cox, Warren M, Jr, Ph D *Mead Johnson & Co, Evansville, Ind Director of Nutritional Research* (2, 1935, 5, 1945)
- Craig, Francis Northrop, M A, Ph D *N Y Univ, 477 First Avenue, New York 16, N Y Instructor, Physiology* (1, 1946)
- Craig, L C, M S, Ph D *Rockefeller Institute, 66th St and York Ave, New York City Associate in Chemical Pharmacology* (2, 1938)
- Crampton, E W, Ph D *Macdonald College, Quebec Canada Professor of McGill University, Nutrition* (5, 1910)
- Crandall, Lathan A, Jr, M D, Ph D *Miles Laboratories, Inc, Elkhart, Indiana* (1, 1930, 5, 1910)
- Cranston, Elizabeth M, B A, M S, Ph D *Dept of Pharmacology, Univ of Minnesota Medical School, Minneapolis 11, Minn Instructor, Dept of Pharmacology* (3, 1946)
- Craver, Bradford N, M A, Ph D, M D *Ciba Pharmaceutical Products, Inc, Lafayette Park, Summit, New Jersey Senior Pharmacologist* (3, 1946)
- Crescitelli, Frederick, Ph B, Sc M, Ph D *Dept of Zoology, Univ of Calif, Los Angeles, Calif Physiologist* (1, 1916)
- Cressy, Norman L, M D *Yale Univ School of Medicine, New Haven, Conn Fellow in Medicine* (6, 1943)
- Cretcher, Leonard H, Ph D *Mellon Institute of Industrial Research, University of Pittsburgh, Pittsburgh, Pa Assistant Director and Head of the Department of Research in Pure Chemistry* (2, 1930)
- Crider, Joseph O, M D *Jefferson Medical College, Philadelphia, Pa Associate Professor of Physiology and Assistant Dean* (1, 1935)
- Crisler, George R, Ph D, M D, V A A F 3036 11th Base, Yuma, Arizona *Captain, Medical Corps* (1, 1930)
- Crismon, Jefferson Martineau, M D *Stanford University, Calif Assistant Professor of Physiology* (1, 1944)
- Crittenden, Phoebe J, M S, Ph D *Merck Institute for Therapeutic Research, Rahway, N J Associate Physiologist* (1, 1937, 3, 1937)
- Cromwell, Hobart W, Sc D *Abbott Laboratories, North Chicago, Ill Manager, Microbiological Research Labs* (6, 1929)
- Crozier, William J, Ph D *Biological Laboratories, Harvard University, Cambridge, Mass Professor of General Physiology* (1, 1928)
- Cruickshank, Ernest W H, M D, D Sc, Ph D *M R C P, F R S E Marischal College, University of Aberdeen, Aberdeen, Scotland Professor of Physiology* (1, 1931)
- Csonka, F A, Ph D *Bureau of Human Nutrition and Home Economics, U S Department of Agriculture, Beltsville, Md Senior Chemist* (2, 1924)
- Cullen, Stuart C, M D *University Hospitals, Iowa City, Iowa Assistant Professor of Surgery-Anesthesia* (3, 1944)
- Culler, Elmer A K, Ph D *University of Rochester, Rochester, N Y Professor of Psychology and Director of the Laboratory* (1, 1936)
- Cunningham, Raymond W, M S, Ph D *Lederle Laboratories, Inc, Pearl River, N Y Head, Pharmacology Research* (3, 1941)

- Cunningham, Robert Sydney**, A M , M D , Sc D
Albany Medical College, Albany, N Y *Professor of Anatomy and Dean* (1, 1923)
- Cureton, Thomas Kirk Jr**, M A , Ph D , B P E ,
M P E Univ of Illinois, School of Physical
Education, Urbana, Ill *Associate Professor of
Physical Education* (1, 1946)
- Curnen, Edward C**, M D Yale Univ School of
Medicine, New Haven 11, Conn (6, 1941)
- Curtis, George Morris**, M A , Ph D , M D Kins-
man Hall, Ohio State University, Columbus
*Professor of Surgery, Chairman, Department of
Research Surgery* (1, 1933, 4, 1933)
- Curtis, Howard J**, M A , Ph D Dept of Physiol-
ogy, Columbia Univ College of Physicians and
Surgeons, New York, 32, N Y (1, 1940)
- Cutler, Elliott C**, M D Peter Bent Brigham
Hospital, Boston, Mass *Moseley Professor of
Surgery, Harvard Medical School, Surgeon-in-
Chief, Peter Bent Brigham Hospital* (4, 1927)
- Cutting, Reginald A**, M D , Ph D Georgetown
University School of Medicine, 3900 Reservoir
Road, N W , Washington, D C *Professor
of Physiology and Director of the Department*
(1, 1939)
- Cutting, Windsor C**, M D Stanford University
School of Medicine, San Francisco, Calif *As-
sistant Professor of Therapeutics* (3, 1939)
- Daft, Floyd Shelton**, Ph D National Institute of
Health, Washington, D C *Senior Scientist* (5,
1941)
- Daggs, Ray Gilbert**, Ph D Armored Medical Re-
search Lab, Fort Knox, Kentucky *Director of
Research* (1, 1935, 5, 1933)
- Dakin, Henry D**, D Sc , LL D , Ph D , F I C ,
F R S Scarborough-on-Hudson, N Y (2,
1906)
- Dalton, Albert J**, M A , Ph D National Insti-
tute of Health, Bethesda, Md *Cytologist*
(4, 1942)
- Dam, Henrik**, D Sc Biokemisk Laboratorier,
Danmarks Tekniske Højskole, Østervoldgade 6 C
Copenhagen, K, Denmark (2, 1944, 5, 1943)
- D'Amour, Fred E**, M S , Ph D 2311 S Josephine
St, Denver, Colo *Associate Professor, Depart-
ment of Zoology, University of Denver* (1, 1934)
- D'Amour, Marie C**, Ph D , M D 2311 So Jose-
phine St, Denver, Colo (1, 1934)
- Daniels, Amy L**, Ph D 720 N Van Buren St ,
Iowa City, Iowa *Retired* (2, 1919, 5, 1933)
- Danielson, Irvin S**, Ph D Pearl River Apart-
ments, Apt 3H, Pearl River, N Y *Research
Chemist* (2, 1937)
- Dann, W J**, Ph D , D Sc Duke University
School of Medicine, Durham, N C *Professor of
Nutrition* (2, 1937, 5, 1938)
- Darby, William J**, M D , Ph D Vanderbilt Univ
School of Medicine, Nashville, Tenn *Associate
Professor of Biochemistry, Assistant Professor
of Medicine* (5, 1945)
- Darling, Robert Croly**, M D 157 Glenwood Ave ,
Leonia, N J Dept of Medicine, Columbia Univ
College of Physicians and Surgeons, New York,
32, N Y (1, 1941)
- Darrow, Chester W**, Ph D Institute for Juve-
nile Research, 907 S Wolcott St, Chicago, Ill
*Research Psychologist, Institute for Juvenile
Research, Associate in Physiology, University
of Illinois College of Medicine* (1, 1937)
- Darrow, Daniel Cady**, M D New Haven Hos-
pital, New Haven, Conn *Associate Professor
of Pediatrics, Yale University* (2, 1936)
- Davenport, Horace Willard**, B S , B Sc (Oxon)
Ph D Dept of Physiology, University of Utah,
Salt Lake City 1 (1, 1942)
- David, Norman Austin**, M D University of
Oregon Medical School, Portland *Professor of
Pharmacology* (3, 1934)
- Davidsohn, Israel**, M D Mount Sinai Hospital,
2750 W 15th Place, Chicago, Ill *Pathologist
and Director of Laboratories, Mt Sinai Hospital,
Associate Professor of Pathology, College of
Medicine, University of Illinois* (4, 1939, 6,
1929)
- Davis, George Kelso**, Ph D Nutrition Laboratory,
Animal Industry Dept, Agricultural Experi-
ment Station, Gainesville, Fla *Nutritional
Technologist and Biochemist, Professor of Nutri-
tion, Univ of Florida, Florida Agricultural
Experiment Station* (5, 1941)
- Davis, Hallowell**, M D Central Institute for the
Deaf, 818 S Kingshighway, St Louis 10, Mo
(1, 1925)
- Davis, Harry A**, M D , C M Dept of Surgery,
College of Medical Evangelists, Boyle and Michi-
gan Avenues, Los Angeles 33, Calif (4, 1944)
- Davis, John Emerson**, M S , Ph D Univ of
Arkansas School of Medicine, Little Rock
Professor of Pharmacology and Physiology (1,
1941, 3, 1941)
- Davson, Hugh**, M Sc , D Sc Dalhousie Univer-
sity, Halifax N S , Canada *Associate Professor
of Physiology* (1, 1941)
- Dawson, Charles R**, Ph D 411 Havemeyer Hall,
Columbia University, New York 27, N Y *Asso-
ciate Professor of Organic Chemistry* (2, 1946)
- Dawson, James Robertson, Jr**, M D Vander-
bilt Medical School, Nashville, Tenn *Professor
of Pathology* (4, 1940)
- Dawson, Percy M**, M D Duke University Medical
School, Durham, N C *Visiting Professor, Dept
of Physiology* (1, 1900)
- Day, Harry G**, D Sc Indiana University,
Bloomington *Associate Professor, Dept of
Chemistry* (5, 1940)
- Day, Paul L**, M A , Ph D University of Ar-
kansas School of Medicine, Little Rock *Pro-
fessor of Physiological Chemistry* (2, 1934, 5,
1933)

- Dearborn, Earl H, M A, Ph D Johns Hopkins Univ School of Medicine, 800 N Washington St, Baltimore 5, Md *Instructor in Pharmacology and Experimental Therapeutics* (3, 1916)
- de Beer, Edwin J, Ph D The Wellcome Research Laboratories, Tuckahoe, N Y *Assistant Director of Research* (3, 1944)
- De Bodo, Richard C, M D 477 First Ave, New York, N Y *Associate Professor of Pharmacology, New York Univ College of Medicine* (1, 1932, 3, 1931)
- DeEds, Floyd, M A, Ph D 314 Santa Ana Ave, San Francisco, Calif *Principal Pharmacologist, Western Regional Research Laboratory, 800 Buchanan St, Albany, Calif* (2, 1937, 3, 1927)
- Defendorf, James Holmes, Ph D Office of the Chief of the Chemical Warfare Service, Washington, D C *Colonel, Sn C* (3, 1940)
- de Gara, Paul F, M D 200 Pinchurst Ave, New York City *Instructor in Pathology, Cornell University Medical College Physician, New York Hospital* (6, 1941)
- DeGraff, Arthur C, M D New York University College of Medicine, New York City *Professor of Therapeutics* (3, 1937)
- de Gutierrez-Mahoney, C G, M D St Vincent's Hospital, New York, N Y *Director, Neurological Division and Neurosurgeon in Chief* (1, 1940, 4, 1941)
- Deichmann, William B, M Sc Ph D 527 McMillan, Cincinnati O *Instructor, Kettering Laboratory of Applied Physiology Instructor in Physiology, University of Cincinnati, College of Medicine* (3, 1941)
- del Pozo, E C, M D Medellin 196, Mexico, D F, Mexico (1, 1943)
- Dempsey, Edward W, Sc M, Ph D Harvard Medical School, Boston, Mass *Instructor in Physiology* (1, 1940)
- Derbyshire, Arthur J, Ph D Wayne University College of Medicine, Detroit, Mich *Associate Professor of Physiology* (1, 1939)
- de Savitsch, Eugene, M D Suite 24, 1150 Connecticut Ave, Washington, D C *Clinical Instructor in Surgery, Georgetown University School of Medicine* (4, 1934)
- Dettwiler, Herman A, M S, Ph D Eli Lilly and Co, Indianapolis, Ind *Research Bacteriologist, Biological Division* (6, 1946)
- Deuel, Harry J, Jr, Ph D University of Southern California Medical School, Los Angeles *Professor of Biochemistry* (1, 1928, 2, 1924, 5, 1933)
- Deulofeu, Venancio, D Chem Casilla Correo 2539, Buenos Aires, Argentina *Professor of Organic Chemistry, University of Buenos Aires* (2, 1942)
- Dey, Frederick L, Ph D, M D 5928 N Paulina St, Chicago, Ill *Lt (j g), USVR* (1, 1945)
- Dickison, H L, M A, Ph D Vanderbilt Univ School of Medicine, Nashville 1, Tennessee *Assistant Professor of Pharmacology* (3, 1946)
- Dienes, Louis, M D Massachusetts General Hospital, Boston *Bacteriologist* (6, 1924)
- Dill, David Bruce, M A, Ph D Fatigue Lab, Soldiers Field, Harvard Univ, Boston, Mass *Professor of Industrial Physiology* (1, 1941, 2, 1927, 5, 1936)
- Dille, James M, M S, Ph D, M D Univ of Washington School of Medicine, Seattle 5, Wash *Professor of Pharmacology, Assistant Dean* (3, 1939)
- Dillon, Robert T, M S, Ph D % G D Searle and Co, Box 5110, Chicago 80, Ill *Head, Analytical Division* (2, 1934)
- Dingle, John H, Sc D, M D Western Reserve University School of Medicine, Cleveland 6, Ohio *Professor of Preventive Medicine* (6, 1941)
- Di Palma, Joseph R, M D Long Island College of Medicine, 350 Henry St, Brooklyn, N Y *Instructor in Medicine* (1, 1943)
- Dische, Zacharias, M D Dept of Biochemistry, College of Physicians and Surgeons, 630 W 168th St, New York City (2, 1944)
- Dixon, Harold M, M D Capt (MC) USNR U S Naval Hospital, Philadelphia 4, Pa *Associate in Pathology, Chief of the Division of Pathology, Phila General Hospital* (4, 1936)
- Doan, Charles A, M D Ohio State University, College of Medicine, Columbus *Dean, Professor of Medicine, Director of Medical Research* (4, 1928)
- Dobriner, Konrad, M D Memorial Hospital, 444 East 68th St, New York 21, N Y *Head, Dept of Research Chemistry, Memorial Hospital for the treatment of Cancer and Allied Diseases* (2, 1946)
- Dochez, A Raymond, M D, Sc D (hon) Presbyterian Hospital, 620 W 168th St, New York City *John E Borne Professor of Medical and Surgical Research, Columbia University, Member of National Academy of Sciences* (4, 1917, 6, 1922)
- Dohan, F Curtis, M D 80 Princeton Rd, Cynwyd, Pa *Fellow, George S Cox Medical Research Institute, Associate in Medicine, University of Pennsylvania, Philadelphia* (1, 1941)
- Doisy, Edward A, M S, Ph D, Sc D St Louis University School of Medicine, St Louis 4, Mo *Professor of Biological Chemistry, Member, National Academy of Sciences* (2, 1920)
- Dominguez, Rafael, M D Saint Luke's Hospital, 11311 Shaker Blvd, Cleveland, O *Director of Laboratories, St Luke's Hospital, Associate in Pathology, Western Reserve University* (1, 1935)
- Donahue, D D, D Sc Division of Industrial Hygiene, National Institute of Health, Md *Physiologist, T Sect.*

- of Industrial Hygiene, U S Public Health Service* (3, 1941)
- Dooley, M S**, M D 766 Irving Ave, Syracuse, N Y *Professor of Pharmacology, College of Medicine, Syracuse University* (3, 1923)
- Dorfman, Ralph I**, Ph D Dept of Biochemistry, Western Reserve University School of Medicine, Cleveland, O *Assistant Professor of Biochemistry* (2, 1940)
- Dotti, Louis Basil**, M A, Ph D St Luke's Hospital, Amsterdam Ave and 113th St, New York City *Chemist, St Luke's Hospital, Lecturer in Physiology and Biochemistry, New York Medical College* (1, 1937)
- Doty, J Roy**, Ph D American Dental Association Bureau of Chemistry, 222 E Superior St, Chicago, Ill *Associate Chemist* (2, 1941)
- Doudoroff, Michael**, M A, Ph D Dept of Bacteriology, 3531 Life Science Bldg, Univ of Calif, Berkeley, Calif *Assistant Professor of Bacteriology* (2, 1946)
- Dounce, Alexander L**, Ph D Strong Memorial Hospital, 260 Crittenden Blvd, Rochester, N Y *Instructor in Biochemistry, University of Rochester, School of Medicine and Dentistry* (2, 1944)
- Dow, Philip**, Ph D University of Georgia School of Medicine, Augusta *Associate Professor of Physiology* (1, 1939)
- Dow, Robert S**, M D, Ph D University of Oregon Medical School, Portland *Associate Professor of Anatomy* (1, 1940)
- Downs, Ardrey W**, M A, M D, D Sc, F A C P University of Alberta, Edmonton, Canada *Professor of Physiology and Pharmacology* (1, 1917)
- Downs, Cora M**, Ph D 1625 Alabama St, Lawrence, Kan (6, 1929)
- Doyle, William Lewis**, M A, Ph D 930 East 58th St, Chicago 37, Ill *Associate Professor of Anatomy* (1, 1946)
- Drabkin, David L**, M D Medical School, University of Pennsylvania, Philadelphia *Associate Professor of Physiological Chemistry* (2, 1928, 5, 1934)
- Dragstedt, Carl A**, Ph D, M D Northwestern University Medical School, 303 E Chicago Ave, Chicago, Ill *Professor of Pharmacology* (1, 1928, 3, 1932)
- Dragstedt, Lester R**, M D, Ph D University of Chicago, Chicago, Ill *Professor of Surgery* (1, 1920)
- Draize, J H**, Ph D Division of Pharmacology, Food & Drug Administration, U S Dept of Agriculture, Washington, D C *Pharmacologist* (3, 1940)
- Drake, T G H**, M B, F R C P (c) University of Toronto, Toronto, Canada *Junior Demonstrator in Paediatrics, Department of Medicine, University of Toronto, Clinical Assistant on Active Staff and Associate Director Research Laboratory, Hospital for Sick Children* (5, 1936)
- Draper, William B**, M Sc, M D University of Colorado School of Medicine, 4200 E 9th Ave, Denver *Associate Professor of Physiology and Pharmacology* (3, 1938)
- Dreisbach, Robert H**, Ph D, M D Stanford University School of Medicine, San Francisco 15, Calif *Instructor On leave Capt, MC, 0491982, Lovell General Hospital, Ft Devens, Mass* (3, 1945)
- Dresbach, Melvin**, M S, M D Hahnemann Medical College, Philadelphia, Pa *Visiting Fellow in Physiology* (1, 1912)
- Dreyer, Nicholas Bernard**, M A (Oxon) School of Medicine, University of Vermont, Burlington *Associate Professor of Physiology and Pharmacology* (3, 1912)
- Drill, Victor Alexander**, Ph D Dept of Pharmacology, Yale University School of Medicine, 333 Cedar St, New Haven, Conn *Instructor in Pharmacology* (1, 1943, 3, 1946)
- Drinker, Cecil K**, M D Harvard University School of Public Health, Boston, Mass *Professor of Physiology and Dean* (1, 1915)
- Drinker, Katherine R**, M D Harvard School of Public Health, 55 Shattuck St, Boston, Mass *Instructor in Public Health* (1, 1915)
- Dripps, Robert D**, M D School of Medicine, University of Pennsylvania, Philadelphia 4 *Assistant Professor of Anesthesiology, Associate in Pharmacology* (3, 1945)
- Driver, Robert L**, Ph D Humboldt, Tennessee (1, 1945)
- Drury, Douglas R**, M D University of Southern California, Los Angeles *Professor of Physiology* (1, 1932)
- Dubin, Harry E**, Ph D 11 W 42nd St, New York 13, N Y *President, H E Dubin Laboratories, Inc* (2, 1925)
- Dubnoff, Jacob W**, M A, Ph D 1871 Bridgen Rd, Pasadena 7, Calif *Research Assistant and Instructor, Calif Institute of Technology* (2, 1946)
- DuBois, Eugene F**, M D Cornell University Medical School, 1300 York Ave, New York, N Y *Professor and Head of the Department of Physiology and Biophysics, Attending Physician, New York Hospital, Member, National Academy of Sciences, Captain (MC) U S N R* (1, 1913, 3, 1921, 5, 1935)
- Du Bois, Kenneth P**, B S, M S, Ph D Dept of Pharmacology, Univ of Chicago, Chicago 37, Ill *Instructor in Pharmacology* (3, 1946)
- Dubos, Rene J**, Ph D, D Sc Rockefeller Institute for Medical Research, 66th St and York

- Ave, New York City *Head, Dept of Bacteriology* (6, 1938)
- Dukes, H H, D V M, M S New York State Veterinary College, Cornell University, Ithaca, N Y *Professor of Veterinary Physiology* (1, 1934)
- Dulaney, Anna D, A M, Ph D Pathological Institute, University of Tennessee, Memphis *Assistant Professor of Bacteriology, Medical School* (6, 1924)
- Dumke, Paul Rudolph, M D Clinical Research Section, Medical Research Lab, Edgewood Arsenal, Edgewood, Md *Instructor in Pharmacology, University of Pennsylvania, Captain, W C* (3, 1942)
- Dunlap, Charles E, M D Tulane University of Louisiana, 1430 Tulane Ave, New Orleans *Professor of Pathology* (4, 1912)
- Dunn, Max Shaw, Ph D University of California, Los Angeles *Professor of Chemistry* (2, 1933)
- Dunn Thelma Brumfield, M D The National Cancer Institute, Bethesda, Md *Research Fellow* (1, 1915)
- Durrant, Edwin Poe, M A, Ph D Ohio State University, Columbus *Associate Professor of Physiology* (1, 1928)
- Dutcher, James D, M S, Ph D The Squibb Institute for Medical Research, New Brunswick, New Jersey *Research Associate, Division of Organic Chemistry* (2, 1946)
- Dutcher, R Adams, M S, M A, D Sc Pennsylvania State College, State College *Professor and Head of Department of Agricultural and Biological Chemistry* (2, 1920, 5, 1933)
- Duval, Charles Warren, M D San José Hospital, San José, Calif *Professor Emeritus of Pathology and Bacteriology, Tulane Univ, New Orleans, La Director, Laboratory of Pathology, San Jose Hospital* (4, 1913)
- du Vigneaud, Vincent, M S, Ph D Cornell University Medical College, 1300 York Ave, New York 21, N Y *Professor of Biochemistry, Member, National Academy of Sciences* (2, 1929, 5, 1934)
- Dworkin, Simon, D D S, M D, C M Biology Building, McGill University, Montreal, Quebec, Canada *Lecturer in Physiology, Faculty of Medicine* (1, 1931)
- Dye, J A, Ph D James Law Hall, Cornell University, Ithaca, N Y *Associate Professor of Physiology* (1, 1929)
- Dye, Marie, M S, Ph D Michigan State College, East Lansing *Dean of Division of Home Economics* (2, 1929, 5, 1933)
- Dyer, Helen M, M S, Ph D National Cancer Institute, U S P H S, Bethesda, Md *Research Fellow* (2, 1936, 5, 1937)
- Eadie, George S, Ph D Duke University School of Medicine, Box 3709, Durham, N C *Professor of Physiology and Pharmacology* (1, 1929, 3, 1940)
- Eagle, Harry, A B, M D Johns Hopkins Univ School of Hygiene and Public Health, 615 N Wolfe St, Baltimore 5, Md *Senior Surgeon, U S Public Health Service, Adjunct Professor of Bacteriology, Johns Hopkins Univ School of Hygiene and Public Health, Medical Officer in Charge, Laboratory of Experimental Therapeutics U S Public Health Service Lecturer in Medicine, Johns Hopkins Medical School* (3, 1916, 1, 1936, 6, 1946)
- Earle, Wilton R, Ph D U S Public Health Service, National Cancer Institute, Bethesda, Md *Principal Cytologist* (4, 1940)
- Eaton, Alonzo Guy, M A, Ph D Louisiana State University Medical Center, New Orleans *Associate Professor of Physiology* (1, 1933)
- Eaton, Monroe D, M D State Department of Public Health, Influenza Laboratory, 1392 University Ave, Berkeley, Calif *Staff Member, International Health Division of The Rockefeller Foundation, Director of Virus Laboratory* (6, 1937)
- Ecker, E E, Ph D School of Medicine, Western Reserve University, 2085 Adelbert Rd, Cleveland, O *Professor of Immunology* (4, 1925)
- Eckstein, Henry C, M S, Ph D 320 W Medical Building, University of Michigan, Ann Arbor *Associate Professor of Biological Chemistry* (2, 1925)
- Eddy, Nathan B, M D National Institute of Health, Bethesda, Md *Principal Pharmacologist, United States Public Health Service* (1, 1919, 3, 1929)
- Eddy, Walter H, A M, Ph D 60 E 42nd St, New York, N Y *Professor Emeritus, Physiological Chemistry, Teachers College, Columbia University* (2, 1913, 5, 1933)
- Edsall, Geoffrey, M D Antitoxin and Vaccine Laboratory, 375 South St, Jamaica Plain, Mass *Acting Director, Division of Biologic Laboratories, Massachusetts Department of Public Health, Associate in Public Health Laboratory Methods, Simmons College, Instructor in Applied Immunology, Harvard School of Public Health* (6, 1943)
- Edsall, John Tileston, M D Harvard Medical School, Boston, Mass *Associate Professor of Biological Chemistry and Tutor in Biochemical Sciences* (2, 1931)
- Edwards, Dayton J, Ph D Cornell University Medical College, 1300 York Ave, New York City *Associate Professor of Physiology, Assistant Dean* (1, 1921)
- Edwards, Jesse E, M D Mayo Clinic, (Sect Path Anat), Rochester 4, Minn (4, 1941)
- Edwards, J Graham, A M, Ph D 24 High St,

- Buffalo, N Y *Assistant Professor of Anatomy, University of Buffalo* (1, 1932)
- Eggerth, Arnold H , Ph D *Hogland Laboratory, 335 Henry St , Brooklyn, N Y Associate Professor of Bacteriology, Long Island College of Medicine* (4, 1925)
- Ehrenstein, Maximilian R , Ph D *806 Maloney Clinic, University of Pennsylvania Hospital, 36th and Spruce Sts , Philadelphia Assistant Professor of Chemistry assigned to Medicine* (2, 1942)
- Ehrich, William E , M D *University of Pennsylvania Medical School, Philadelphia Assistant Professor of Pathology, Graduate School of Medicine, Phila Professor of Histology, Chief, Division of Pathology, Phila General Hospital* (4, 1945)
- Eichelberger, Lillian, Ph D *University of Chicago, Dept of Medicine, Chicago, Ill Associate Professor of Biochemistry* (2, 1937)
- Eiseman, Anna J , Ph D *U S Public Health Service Hospital, Lexington, Ky Biological Chemist* (2, 1930)
- Elderfield, Robert C , Ph D *Columbia University, New York City Professor of Chemistry* (2, 1934)
- Elftman, Herbert, M A , Ph D *College of Physicians and Surgeons, Columbia University, 630 W 168th St , New York City Assistant Professor in Anatomy* (1, 1940)
- Eliot, Martha M , M D *United States Children's Bureau, Washington 25, D C Associate Chief* (5, 1933)
- Elliott, K Allan C , M Sc , Ph D *Montreal Neurological Institute, 3801 University St , Montreal, Canada Assistant Professor in Neurology, Biochemistry, McGill University* (2, 1937)
- Ellis, Frederick W , M D *Monson, Mass* (1, 1887)
- Ellis, Fred W , M S , Ph D *University of North Carolina, Chapel Hill Assistant Professor of Pharmacology* (3, 1945)
- Ellis, Lillian N , Ph D *Adelphi College, Garden City, N Y* (5, 1940)
- Ellis, Max Mapes, A M , Ph D , Sc D *Medical School, University of Missouri, Columbia Professor of Physiology and Pharmacology* (1, 1923)
- Ellis, N R , M S *Bureau of Animal Industry, U S Department of Agriculture, Agricultural Research Center, Beltsville, Md Principal Chemist, Animal Husbandry Division* (2, 1928, 5, 1933)
- Elser, William J , M D *Kent, Conn* (6, 1920)
- Elvehjem, Conrad Arnold, M S , Ph D , Sc D *Biochemistry Building, University of Wisconsin, Madison Chairman, Dept of Biochemistry, Dean of Graduate School, Member, National Academy of Sciences* (2, 1931, 5, 1933)
- Embrece, Norris Dean, Ph D *755 Ridge Road West, Rochester 13, N Y Assistant Director of Research, Distillation Products, Inc* (2, 1946)
- Emerson, George A , M S , Ph D *University of Texas, Medical Branch, Galveston Professor of Pharmacology* (3, 1935)
- Emerson, Gladys A , Ph D *Merck Institute of Therapeutic Research, Rahway, N J Nutritionist* (5, 1912)
- Emerson, Oliver H , Ph D *Western Regional Research Laboratory, U S Dept of Agriculture, Albany 6, Calif Associate Chemist* (2, 1938)
- Emery, Frederick E , D V M , M S , Ph D *University of Arkansas School of Medicine, Little Rock Professor of Physiology and Pharmacology* (1, 1930)
- Emmett, Arthur D , M A , Ph D *Star Route 1, Lewiston, Mich* (2, 1908, 5, 1933)
- Enders, John F , A M , Ph D *Department of Bacteriology, Medical School, Harvard University, Boston, Mass Assistant Professor of Bacteriology and Immunology* (6, 1936)
- Engle, Earl Theron, Ph D *College of Physicians and Surgeons, Columbia University, 630 W 168th St , New York City Professor of Anatomy* (1, 1930)
- English, James, Jr , Ph D *Sterling Chemistry Laboratory, Yale Univ , New Haven, Conn Assistant Professor of Chemistry* (2, 1946)
- Epstein, Albert A , M D *1111 Madison Ave , New York City Physician, Beth Israel Hospital, Physician, Hospital for Joint Diseases* (2, 1912)
- Erickson, Cyrus C , M D *Duke University School of Medicine, Durham, N C Associate Professor of Pathology* (4, 1941)
- Erickson, John Otto, Ph D *Physics Division, American Cyanamid Company, Stamford, Conn Research Biochemist* (6, 1946)
- Erlanger, Joseph, M D , LL D , Sc D *Washington University School of Medicine, 4580 Scott Ave , St Louis, Mo Emeritus Professor of Physiology, Member of the National Academy of Sciences* (1, 1901)
- Eschenbrenner, Allen B , M D *Surgeon USPHS, National Institute of Health, Bethesda 14, Md* (4, 1946)
- Espe, Dwight L , Ph D *Iowa State College, Ames Assistant Research Professor in Dairy Husbandry* (1, 1940)
- Essex, Hiram E , M S , Ph D *Mayo Foundation, Rochester, Minn Professor of Physiology, Institute of Experimental Medicine* (1, 1932, 3, 1940)
- Ettinger, C H , M D , C M , F R S C *Queen's University, Kingston, Canada Professor of Physiology* (1, 1943)

- Evans, Earl Alison, Jr., Ph D Department of Biochemistry, University of Chicago, Chicago, Ill Professor and Chairman of Department (2, 1939)
- Evans, Everett Idris, M D, Ph D Department of Surgery, Medical College of Virginia, Richmond Assistant Professor of Surgery (1, 1935)
- Evans, Gerald Taylor, M D, Ph D University of Minnesota Hospitals, Minneapolis Director of Laboratory Service, University of Minnesota Hospitals, Associate Professor of Medicine, University of Minnesota (1, 1912)
- Evans, Herbert M., M D University of California, Berkeley Professor of Anatomy and Director of Institute of Experimental Biology, Member of the National Academy of Sciences (1, 1919)
- Eveleth, D F., Ph D, D V M North Dakota Agricultural College, Fargo Professor, Veterinary Science, North Dakota Agricultural Experiment Station (2, 1939)
- Everett, Mark Reuben, Ph D University of Oklahoma Medical School, Oklahoma City Professor of Biochemistry (2, 1929)
- Ewing, P L., M S, Ph D University of Texas School of Medicine, Galveston Associate Professor of Pharmacology (3, 1938)
- Eyster, John A English, M D University of Wisconsin, Madison Professor of Physiology (1, 1906, 3, 1908)
- Fahr, George, M D Minneapolis General Hospital Minneapolis Professor of Clinical Medicine, University of Minneapolis Medical School (1, 1913, 3, 1940)
- Faile, Crawford F., Ph D 5454 South Shore Drive, Chicago 15, Ill Associate Professor of Biochemistry, University of Chicago (2, 1933)
- Fairhall, Lawrence T., M A, Ph D U S Public Health Service, Washington, D C Principal Industrial Toxicologist (2, 1924)
- Falk, Carolyn R., B A 40 E 66th St, New York City Bacteriologist, Bureau of Laboratories, New York City Dept of Health (6, 1943)
- Falk, K George, Ph D 40 E 66th St, New York City Director, Laboratory of Industrial Hygiene (2, 1913)
- Famulener, Lemuel W., Ph C, M D 275 Engle St, Englewood, N J (6, 1920)
- Farber, Sidney, M D Harvard Medical School, 25 Shattuck St, Boston, Mass Assistant Professor of Pathology (4, 1934)
- Farmer, Chester J., A M Northwestern Medical School, 303 E Chicago Ave, Chicago, Ill Professor of Chemistry (2, 1935)
- Farr, Lee E., M D Alfred I duPont Institute, Wilmington, Del Director of Research, Pediatrician in Chief (4, 1941)
- Farrell, James I., Ph D, M D 934 Ridgeway Ave, Evanston, Illinois (1, 1938)
- Fassett, David W., A B, M D 306 Huntington Building, Miami, Fla (3, 1912)
- Favorite, Grant O., M D 1313 Andover Rd, Overbrook, Philadelphia, Pa Pathologist, West Jersey Hospital, Associate in Bacteriology and Immunology, Jefferson Medical College (6, 1913)
- Fay, Marion, M A, Ph D Woman's Medical College of Pennsylvania, East Falls, Philadelphia 29 Professor of Physiological Chemistry (2, 1937)
- Feldman, Harry A., M D Major MC, AUS, 1722 -33rd Place, S E, Washington 20, D C (6, 1913)
- Feldman, William H., D V M, M S The Mayo Foundation, Rochester Minn Professor in the Division of Experimental Surgery and Pathology (4, 1934)
- Fell, Norbert, Ph D Camp Detrick, Frederick, Maryland Chief, Pilot Plant Division (6, 1944)
- Feller, A E., M D Western Reserve School of Medicine, Cleveland 6, Ohio Assistant Professor of Preventive Medicine (6, 1943)
- Fellows, Edwin J., M S, Ph D Temple University School of Medicine, Philadelphia, Pa Assistant Professor of Pharmacology (3, 1939)
- Felton, Lloyd D., M D, D Sc National Institute of Health, Bethesda, Md Medical Director, USPHS (6, 1926)
- Fenn, Wallace Osgood, A M, Ph D University of Rochester School of Medicine and Dentistry, 260 Crittenden Blvd, Rochester, N Y Professor of Physiology, Member, National Academy of Sciences (1, 1924)
- Fenning, Con, M D, M A University of Utah School of Medicine, Salt Lake City Professor of Pharmacology and Physiology (1, 1942)
- Ferguson, James Kenneth Wallace, M A, M D 76 Kilbarry Rd, Toronto, Ontario, Canada Professor of Pharmacology, University of Toronto Wing Commander, R C A F (1, 1933, 3, 1941)
- Ferguson, John Howard, M D, M A, L M S S A Dept of Physiology, School of Medicine, University of North Carolina, Chapel Hill Professor of Physiology and Acting Professor of Pharmacology (1, 1933, 3, 1939)
- Ferguson, L Kraeer, M D 133 S 36th St, Philadelphia 4, Pa Professor of Surgery, Graduate School, Univ of Pennsylvania, and Woman's Medical College of Pennsylvania, Surgeon, Doctors Hospital and Woman's Medical College, Graduate Hosp, Philadelphia General Hospital (4, 1935)
- Ferry, John Douglas, Ph D, Dept of Chemistry,

- Univ of Wisconsin, Madison 6, Wis *Assistant Professor of Chemistry* (2, 1911)
- Ferry, Newell S, M D, Parke, & Davis Co Detroit, Mich *Assistant Director of Research* (6, 1916)
- Ferry, Ronald M, M D 966 Memorial Drive Cambridge, Mass, Master of John Winthrop House, *Associate Professor of Biochemistry*
- Fletcher, Edwin S, Ph D R D #1, Xenia, Ohio (1, 1944)
- Fetter, Dorothy, Ph D Department of Hygiene, Brooklyn College, Brooklyn, N Y *Instructor in Physiology* (1, 1944)
- Fevold, Harry L, M S, Ph D Western Regional Research Laboratory, Albany 6, Calif *Biochemist in Charge, Pharmaceutical, Food Proteins and Lipids Section, U S Dept of Agriculture* (2, 1942)
- Field, John, II, A M, Ph D Stanford University, Stanford, Calif *Professor of Physiology* (1, 1930)
- Fincke, Margaret L, Ph D Oregon State College, Corvallis *Associate Professor of Foods and Nutrition, School of Home Economics* (5, 1940)
- Findley, Thomas, Jr, M D Ochsner Clinic, 3503 Prytania, New Orleans, La *Head of the Department of Internal Medicine, Ochsner Clinic, New Orleans, Assistant Professor of Clinical Medicine, Tulane University School of Medicine* (1, 1938)
- Finland, Maxwell, B S Boston City Hospital, Boston, Mass *Assistant Professor of Medicine, Harvard Medical School* (6, 1941)
- Firor, Warfield Monroe, M D Johns Hopkins Hospital, Baltimore, Md *Associate Professor of Surgery, Johns Hopkins University* (1, 1932)
- Fischer, Ernst, M D, Dr habil Medical College of Virginia, Richmond *Professor of Physiology* (1, 1936)
- Fischer, Hermann O L, Ph D Banting Institute, 100 College St, University of Toronto, Toronto 5, Canada *Research Professor of Organic Chemistry* (2, 1940)
- Fischer, Martin H, M D, Pharm D (hon), Sc D University of Cincinnati College of Medicine, Eden Ave, Cincinnati 19, O *Professor of Physiology* (1, 1901, 2, 1919)
- Fishberg, Ella H, M A, M D Beth Israel Hospital, Stuyvesant Park East, New York City *Biochemist* (2, 1931)
- Fisher, Albert Madden, M A, Ph D Connaught Laboratories, University of Toronto, Toronto, Canada *Research Associate* (2, 1944)
- Fisher, Kenneth C, M A, Ph D University of Toronto, Toronto, Ont, Canada *Assistant Professor of Physiological Zoology* (1, 1940)
- Fiske, Cyrus H, M D Harvard Medical School, Boston, Mass *Professor of Biological Chemistry* (2, 1914)
- Fitzgerald, Mabel P, 51 A, George Sq, Edinburgh, Scotland (1, 1913)
- Fitzhugh, O Garth, Ph D Division of Pharmacology, Food and Drug Administration, Federal Security Agency, Washington, D C *Pharmacologist* (3, 1910)
- Fleischmann, Walter, M D, Ph D Harriet Lane Home, Johns Hopkins Hospital, Baltimore, Md *Associate in Pediatrics, Johns Hopkins University* (1, 1910)
- Fleisher, Moyer S, M D Jewish Hospital, St Louis, Mo *Research Bacteriologist* (4, 1921, 6, 1932)
- Flexner, Louis B, M D Department of Embryology, Carnegie Institution of Washington, Wolfe and Madison Sts, Baltimore, Md *Research Associate* (1, 1933)
- Flock, Eunice V, Ph D Mayo Clinic, Rochester, Minn *Associate Professor in Experimental Medicine, Mayo Foundation, Univ of Minnesota* (2, 1910)
- Florman, Alfred L, M D Hospital of the Rockefeller Institute, New York, N Y *Visiting Investigator* (6, 1912)
- Flosdorf, Earl W, Ph D Forest Grove, Bucks Co, Pa *Research—University of Pennsylvania School of Medicine* (6, 1941)
- Floyd, Cleveland, M D, Sc D 246 Marlborough St, Boston, Mass *Chief Examiner, Boston Health Dept* (6, 1916)
- Foa, Piero Pio, Ph D 710 S Wolcott St, Chicago Ill *Associate Professor of Physiology and Pharmacology, Chicago Medical School* (1, 1944)
- Folch, Jordi, M D McLean Hospital, Waverly, Mass *Assistant Professor of Biological Chemistry, Harvard Medical School Director of Scientific Research, McLean Hospital* (2, 1941)
- Follensby, Edna M, Ph G 80 E Concord St, Boston, Mass *Research Assistant, Evans Memorial Special Instructor in Biology, Simmons College* (6, 1933)
- Follis, Richard H, Jr, M D Duke Univ Medical School, Durham, N C *Associate Professor of Pathology* (4, 1942)
- Fontaine, Thomas Davis, Ph D Biologically Active Compounds Division, Room 114 North Bldg, Agricultural Research Center, Beltsville, Md *Chemist, Bureau of Agricultural and Industrial Chemistry, U S Dept of Agriculture* (2, 1946)
- Foot, Nathan Chandler, M D 340 E 72nd St, New York City *Professor of Surgical Pathology, Cornell University Medical College, Surgical Pathologist, New York Hospital* (4, 1924)
- Forbes, Alexander, A M, M D Harvard Medical School, Boston, Mass *Professor of Physiology, Member of the National Academy Sciences* (1, 1910)
- Forbes, Ernest B, Ph D State College, Pa

- Director of the Institute of Animal Nutrition* (1, 1917, 5, 1935)
- Forbes, Henry S, M D Forest St, Milton, Mass Associate in Neuropathology, Harvard Medical School, Boston (1, 1931)
- Forbes, John C, M A, Ph D Medical College of Virginia, Richmond Research Professor of Biochemistry (2, 1937)
- Forbes, William H, M A, Ph D Harvard University, Fatigue Laboratory, Boston, Mass Research Fellow, Assistant Director of Fatigue Lab, Assistant Professor of Industrial Physiology (1, 1943)
- Fosdick, Leonard S, Ph D 311 E Chicago Ave, Chicago, Ill Professor of Chemistry, Northwestern University (2, 1944)
- Foster, G L, Ph D College of Physicians and Surgeons, 630 W 168th St, New York City Professor of Biological Chemistry (2, 1923)
- Foster, Harry E, M D Cutter Laboratory, Berkeley, Calif Medical Director (6, 1913)
- Foster, Jackson W Dept of Botany and Bacteriology, Univ of Texas Austin 12, Texas Associate Professor of Bacteriology (2, 1946)
- Foster, Robert H K, Ph D M D St Louis University School of Medicine, St Louis, Mo Associate Professor of Pharmacology (1, 1940, 3, 1944)
- Foster, Ruth A C, Ph D Dept of Botany and Bacteriology, University of Texas, Austin Instructor (6, 1943)
- Fothergill LeRoy D, M D Camp Detrick, Frederick, Maryland (6, 1936)
- Fox, Sidney W, Ph D Chemistry Dept, Iowa State College, Ames, Iowa Assistant Professor of Chemistry and Research Assistant Professor, Chemistry Section, Iowa Agricultural Experiment Station (2, 1946)
- Fraenkel-Conrat, Heinz, M D, Ph D Western Regional Research Laboratory, U S Dept of Agriculture, Albany 6, Calif Chemist (2, 1942)
- Francis, Thomas, Jr, M D, M S (hon), Sc D (hon) School of Public Health, University of Michigan, Ann Arbor Professor of Epidemiology (4, 1940, 6, 1930)
- Franke, Florent E, M D 9 Sylvester, Webster Groves, Mo Assistant Professor of Physiology, St Louis University School of Medicine (1, 1934)
- Frankel, Edward M, Ph D 214 River Rd, N Yack, N Y Consulting Chemist (2, 1916)
- Fraser, Alexander MacLeod, A M, M D, C M McGill University, Montreal, Canada Lecturer in Pharmacology (3, 1939)
- Fraser, Donald T, M B Connaught Laboratories, University of Toronto, Toronto 5, Canada
- Professor of Hygiene and Preventive Medicine* (6, 1935)
- Frear, Donald E, M S, Ph D Dept of Agricultural and Biological Chemistry The Pennsylvania State College, State College, Pa Professor of Agriculture and Biological Chemistry (2, 1946)
- Free, Alfred H School of Medicine, Western Reserve University, Cleveland, O Asst Professor of Biochemistry (5, 1944, 2, 1946)
- Freeman, Harry, M D Worcester State Hospital, Worcester, Mass Internist, Research Service (1, 1939)
- Freeman, Leslie Willard, Ph D, M D 1631—18th St C Moline, Ill Capt, Medical Corps, A US (1 1944)
- Freeman, Norman E, M D 263 Moline Ave, Mill Valley, Calif (1, 1936)
- Freeman, Smith, M D, Ph D Northwestern University School of Medicine, 303 E Chicago Ave, Chicago, Ill Assistant Professor of Physiology and Pharmacology (1, 1937)
- French, C S, Ph D, Dept of Botany, Univ of Minnesota, Minneapolis, 14, Minn Associate Professor (2, 1946)
- Freund, Jules, M D Public Health Research Institute of the City of New York, Foot of E 15th St, New York, N Y Member (4, 1930, 6, 1924)
- Friedemann, Theodore E, M A, Ph D Northwestern University Medical School, 303 E Chicago Ave, Chicago, Ill Associate Professor of Physiology (2, 1925)
- Friedemann, Ulrich, M D Department of Bacteriology, The Jewish Hospital of Brooklyn, Classon and St Marks Ave, Brooklyn, N Y (6, 1938)
- Friedewald, William F, M D Emory University School of Medicine, Atlanta, Ga Professor of Bacteriology, Associate Professor of Medicine (4, 1941)
- Friedgood, Harry B, M D 2943 Queensburg Road, Los Angeles 34, Calif Assistant Clinical Professor of Medicine, Univ of Southern Calif Med School, Senior Attending Physician, Los Angeles County Hospital (1, 1936)
- Friedman, Maurice H, Ph D, M D Hunter Field Regional Hospital Hunter Field, Ga Captain (MC) A US, Chief, Gastro enterology (1, 1929)
- Friedman, M H F, M A, Ph D Jefferson Medical College of Philadelphia, 1025 Walnut St, Philadelphia, Pa Assistant Professor of Physiology (1, 1941)
- Friedman, Nathan B, M D Army Institute of Pathology, 7th and Independence, S W, Washington 25, D C (4, 1942)
- Frisch, Arthur W, Ph D, M D College of Medicine, Wayne University, Detroit, Mich Instructor (6, 1938)

- Frost, Douglas Van Anden, M A , Ph D Abbott Laboratories, North Chicago, Ill *Director, Nutritional Research Division* (2, 1916)
- Fruton, J S , Ph D Yale School of Medicine, 333 Cedar St , New Haven, Conn *Associate Professor of Physiological Chemistry* (2, 1938)
- Fugo, Nicholas W , M S , Ph D State University of Iowa, Medical School, Iowa City *Instructor in Pharmacology, on leave* (3, 1944)
- Fuhrman, Frederick A , M S , Ph D Dept of Physiology, Stanford Univ , Stanford University, Calif *Instructor in Physiology* (1, 1916)
- Fulton, John Farquhar, M A , Ph D , M D Yale University School of Medicine, New Haven, Conn *Sterling Professor of Physiology* (1, 1925)
- Funk, Casimir, D Sc , Ph D 186 Riverside Drive, New York 24, N Y (2, 1921)
- Furth, Jacob, M D Cornell University Medical College, 1300 York Ave , New York City *Professor of Pathology* (4, 1932, 6, 1930)
- Gaebler, Oliver H , Ph D , M D Henry Ford Hospital, Detroit, Mich *Associate in Chemistry* (2, 1927)
- Gaffron, Hans, Ph D Chemical Department, University of Chicago, Chicago, Ill *Research Associate (Assistant Professor)* (2, 1941)
- Gagge, Adolf Pharo, Ph D Aeromedical Research Laboratory, Wright Field, Dayton, O *Lt Col , Chief, Biophysics Branch, Air Corps, U S Army, on leave from Yale University and John B Pierce Laboratory of Hygiene* (1, 1939)
- Galambos, Robert, M A , Ph D University of Rochester School of Medicine and Dentistry, 260 Crittenden Blvd , Rochester, N Y (1, 1942)
- Gall, Edward A , M D Bethesda Hospital, Cincinnati, O *Assistant Professor of Pathology, College of Medicine, University of Cincinnati* (4, 1941)
- Gallagher, Thomas F , Ph D University of Chicago, Chicago, Ill *Associate Professor of Biochemistry* (2, 1932)
- Gallup, Willis D , M S , Ph D Oklahoma Agricultural and Mechanical College, Stillwater *Chemist and Professor of Agricultural Chemistry* (2, 1932)
- Gamble, James L , M D , S M 33 Edgehill Rd , Brookline, Mass *Professor of Pediatrics, Harvard Medical School* (2, 1922, 5, 1933)
- Gantt, W Horsley, M D Phipps Psychiatric Clinic, Johns Hopkins Hospital, Baltimore, Md *Associate in Psychiatry* (1, 1935)
- Garbat, Abraham L , M D 103 E 78th St , New York City *Attending Physician, Lenox Hill Hospital* (6, 1913)
- Garrey, Walter Eugene, Ph D , M D Vanderbilt University School of Medicine, Nashville, Tenn *Professor Emeritus of Physiology* (1, 1910, 2, 1906)
- Gasser, Herbert S , A M , M D , Sc D (hon) Rockefeller Institute for Medical Research, 66th St and York Ave , New York City *Director of Laboratories, Member of the National Academy of Sciences* (1, 1915, 3, 1921)
- Gates, Olive, M D 25 Shattuck St , Boston, Mass *Associate Pathologist* (4, 1910)
- Gaunt, Robert, Ph D Washington Square College, New York University, New York City *Associate Professor of Biology* (1, 1939)
- Gay, Leslie N , M D 1114 St Paul St , Baltimore, Md *Director of the Allergy Clinic, Johns Hopkins Hospital, Visiting Physician to Johns Hopkins Hospital, Associate in Medicine, Johns Hopkins University* (6, 1927)
- Geiling, E M K , M S , M D , Ph D University of Chicago, Chicago, Ill *Frank P Hixon Distinguished Service Professor of Pharmacology and Chairman of Department* (1, 1933, 2, 1927, 3, 1925)
- Gelfan, Samuel, Ph D College of Physicians and Surgeons, Columbia University, 630 West 168th St , New York 32, N Y *Assistant Professor of Physiology* (1, 1930)
- Gellhorn, Alfred, M D Dept of Pharmacology, College of Physicians and Surgeons, 630 West 168th St , New York, 32, N Y *Associate Professor of Pharmacology* (3, 1946)
- Gellhorn, Ernst, M D , Ph D Room 116, Medical Sciences, University of Minnesota, Minneapolis *Professor of Neurophysiology* (1, 1930)
- Gemmull, Chalmers L , M D Medical School, University of Virginia, Charlottesville *Professor of Pharmacology* (1, 1928, 2, 1935, 3, 1946)
- Gerard, R W , Ph D , M D University of Chicago, Chicago, Ill *Professor of Physiology* (1, 1927)
- Gerstenberger, Henry John, M D Western Reserve University, Cleveland, O *Professor Emeritus of Pediatrics, School of Medicine, Western Reserve University, Director of Pediatrics, Babies and Children's Hospital* (5, 1938)
- Gesell, Robert, M D University of Michigan, Ann Arbor *Professor of Physiology* (1, 1913)
- Gettler, Alexander O , A M , Ph D , LL D New York University, 29 Washington Place, New York City *Professor of Chemistry and Toxicology, Toxicologist to Chief Medical Examiner's Office* (2, 1916)
- Gey, George Otto, M D Division for Cellular Pathology, Room 531, Dispensary Building, Johns Hopkins Hospital and University, Baltimore 5, Md *Instructor in Surgery* (1, 1940)
- Gibbs, Frederick Andrews, M D 720 N Michigan Ave , Suite 610, Chicago, Ill (1, 1935)

- Gibbs, Owen Stanley, M B , Ch B (Edin), M D 1514-46 Netherwood, Memphis 6, Tenn *Research Consultant* (1, 1935, 3, 1930)
- Gibson, Robert Banks, Ph D University Hospital, Iowa City, Iowa *Associate Professor of Biochemistry, State University of Iowa* (1, 1907, 2, 1906)
- Gies, William John, M S , Ph D , Sc D , LL D , F A C D 632 W 168th St , New York City *Professor of Biological Chemistry, Columbia University* (1, 1898, 2, 1906, 3, 1909)
- Gilbert, Ruth, A M , M D R F D 2, Altamont, N Y *Bacteriologist, New York State Department of Health, Albany* (6, 1920)
- Gilman, Alfred, Ph D College of Physicians and Surgeons, 630 West 168th St , New York 32, N Y *Associate Professor of Pharmacology* (1, 1935, 3, 1934)
- Gilson, Arthur S , Jr , A M , Ph D Washington University Medical School, St Louis, Mo *Associate Professor of Physiology* (1, 1927)
- Githens, Thomas Statesbury, M D The Cambridge, Wissahickon and Chelton Aves , Germantown, Philadelphia, Pa (1, 1915)
- Givens, Maurice H , Ph D Box 3836, Peninsula Station, Daytona Beach, Fla (1, 1917, 2, 1915)
- Glaser, O C , Ph D Amherst College, Amherst, Mass *Professor of Biology* (1, 1913)
- Glazko, Anthony J , Ph D Box 729, Emory University, Georgia *Assistant Professor of Biochemistry, Medical School* (1, 1942)
- Click, David, Ph D Dept of Physiology, Miller Hall, University of Minnesota, Minneapolis 14, Minn *Associate Professor of Physiological Chemistry and Consultant to Veteran's Hospital*, (2, 1936)
- Goebel, Walther F , Ph D The Rockefeller Institute for Medical Research, 66th St and York Ave , New York City *Member* (2, 1929, 6, 1937)
- Goerner, Alfred, Ph G , Pharm D , M D 366 Sterling Place, Brooklyn, N Y *Assistant Clinical Professor of Medicine, Long Island College of Medicine* (2, 1939)
- Goettsch, Marianne, Ph D School of Tropical Medicine of Columbia University, San Juan, Puerto Rico *Assistant Professor of Chemistry* (2, 1933, 5, 1941)
- Gold, Harry, M D 1300 York Ave , New York City *Assistant Professor of Pharmacology, Cornell Medical College* (3, 1927)
- Goldblatt, Harry, M D Director Institute for Medical Research, Cedars of Lebanon Hospital, Los Angeles, Calif (1, 1945, 4, 1927)
- Goldfarb, Walter, M D 120 Station Hospital, A P O 508, New York, N Y *Captain, M C* (1, 1938)
- Goldforb, A J , Ph D College of the City of New York, New York City *Professor of Biology* (1, 1930)
- Goldie, Horace, M D , D T M Nanuet, N Y City of New York, Dept of Health (6, 1943)
- Goldring, William, M D New York University College of Medicine, 477 First Ave , New York City *Professor of Medicine* (1, 1939)
- Goldschmidt, Samuel, Ph D University of Pennsylvania Medical School, Philadelphia *Associate Professor of Physiology* (1, 1919, 2, 1915)
- Goldsmith, Grace A Tulane University of Louisiana, New Orleans (5, 1943)
- Golub, Orville Joseph, M S , Ph D Lt Cmdr IIS, USNR, Camp Detrick, Frederick, Md *Research Bacteriologist (Viruses)* (6, 1944)
- Goodman, Louis Sanford, M A , M D University of Utah School of Medicine, Salt Lake City *Professor of Pharmacology and Chairman of the Department of Pharmacology and Physiology* (3, 1937, 1, 1946)
- Goodner, Kenneth, Ph D Jefferson Medical College, Philadelphia, Pa *Professor of Bacteriology* (6, 1932)
- Goodpasture, Ernest William, M D Vanderbilt University Medical School, Nashville, Tenn *Professor of Pathology and Dean* (4, 1923)
- Gordon, Albert S , M S , Ph D Washington Square College of Arts and Sciences, New York University, New York City *Assistant Professor of Biology* (1, 1942)
- Gordon Harry H , M D 4200 E 9th Ave , Denver, Colo *Professor of Pediatrics, University of Colorado Medical School, Pediatrician in Chief, Colorado General Hospital* (5, 1940)
- Gordon, Irving, M D Division of Laboratories & Research, N Y State Dept of Health, New Scotland Ave , Albany 1, N Y *Senior Medical Bacteriologist* (6, 1943)
- Gordon, William G , M A , Ph D Eastern Regional Research Laboratory, U S Department of Agriculture, Chestnut Hill Station, Philadelphia, Pa *Chemist* (2, 1939)
- Goss, Harold, Ph D University of California College of Agriculture, Davis *Professor of Animal Husbandry* (2, 1936, 5, 1933)
- Gottschall, Russell Y , M S , Ph D Bureau of Laboratories, Michigan Department of Health, Lansing *Bacteriologist* (6, 1939)
- Goudsmit, Arnoldus, Jr , M D , Ph D 40 Roberts Avenue, Glenside, Pa Medical Corps, 232 General Hospital, Camp Berkeley, Texas (1, 1940)
- Govier, William M , M D Sharp and Dohme, Inc , Glenolden, Pa *Pharmacologist—Medical-Research Division* (3, 1944)
- Grabfield, G Philip, M D 27 Forest St , Milton, Mass *Associate in Medicine and Pharmacology, Harvard Medical School (At present on leave of absence, Col M C , U S A)* (3, 1923)

- Grady, Hugh G**, M D Jefferson Medical College, Philadelphia, Pa *Assistant Professor of Pathology* (4, 1940)
- Graef, Irving**, M D 360 East 55th, New York, N Y *Associate Professor of Pathology, Associate Visiting Physician, 3rd (NYU) Medical Division, Goldwater Memorial Hospital, Attending Consultant in Medicine, Veteran's Hospital, Bronx, N Y* (4, 1941)
- Graham, Clarence H**, Ph D Columbia University, New York 27, N Y *Professor of Psychology* (1, 1933)
- Graham, Helen Tredway**, A M, Ph D Euclid Ave and Kingshighway, St Louis, Mo *Associate Professor of Pharmacology, Washington University School of Medicine* (1, 1933, 3, 1931)
- Grant, R Lorimer**, M S, Ph D Division of Pharmacology, Food and Drug Administration, Federal Security Agency, Washington 25, D C *Pharmacologist* (2, 1938)
- Graubard, Mark**, M A, Ph D 3427 Oakwood Ter, N W, Washington, D C *Research Associate* (1, 1940)
- Grauer, Robert C**, M D Allegheny General Hospital, Pittsburgh, Pa *Head of Department of Research in Endocrinology and Metabolism, William H Singer Memorial Research Laboratory, Lecturer in Pathology and Instructor in Medicine, School of Medicine, University of Pittsburgh* (4, 1941)
- Gray, John S**, M S, Ph D Northwestern Univ Medical School, 303 E Chicago Ave, Chicago 11, Ill *Associate Professor of Physiology* (1, 1937)
- Gray, M Geneva**, M A, Ph D Laboratories of Arthur D Little, Inc, Cambridge, Mass *Director Pharmacological Research* (3, 1946)
- Gray, Samuel H**, M D The Jewish Hospital of St Louis, Kingshighway and Forest Park Blvd, St Louis, Mo *Pathologist, Jewish Hospital, Director of Laboratories, City Hospitals, Associate Professor of Pathology, Washington University* (4, 1939)
- Greaves, J D**, M S, Ph D Western Regional Research Lab, U S Dept of Agriculture, 800 Buchanan St, Albany 6, Calif *Biochemist* (2, 1938)
- Greaves, Joseph E**, Ph D Utah State Agricultural College, Logan *Professor and Head of Department of Bacteriology and Biochemistry* (2, 1940)
- Greeley, Paul O**, A M, Ph D, M D University of Southern California Medical School, University Park, Los Angeles *Dept of Aviation Medicine* (1, 1940)
- Green, Arda Alden**, M D Cleveland Clinic, Euclid and E 93rd St, Cleveland 6, O *Research Division* (2, 1932)
- Green, Daniel M**, M D Kings County Hospital, Seattle, Wash *Instructor, Pharmacology and Therapeutics, University of Tennessee (on leave) Lt Col O 291385, M C* (3, 1942)
- Green, David E**, Ph D Department of Medicine, College of Physicians and Surgeons, Columbia University, New York City *Assistant Professor* (2, 1941)
- Green, Harold David**, M D Bowman Gray School of Medicine, Wake Forest College, Winston-Salem 7, N C *Professor of Physiology and Pharmacology* (1, 1936, 3, 1945)
- Green, Robert**, M A, M D 223 Millard Hall, University of Minnesota, Minneapolis *Professor of Bacteriology and Immunology* (6, 1930)
- Greenberg, David Morris**, Ph D University of California, Berkeley *Professor of Biochemistry, Chairman of Division* (2, 1927, 5, 1946)
- Greenberg, Louis D**, Ph D Univ of Calif Medical Center, 3rd and Parnassus Aves, San Francisco 22, Calif *Assistant Professor of Pathology and Pharmacology* (2, 1946)
- Greene, Carl Hartley**, Ph D, M D 401 Clinton Ave, Brooklyn, N Y *Associate Professor of Clinical Medicine, New York Post-Graduate Medical School of Columbia University, Clinical Professor of Medicine, Long Island College of Medicine* (1, 1921, 2, 1922, 4, 1924)
- Greene, Charles Wilson**, A M, Ph D 814 Virginia Ave, Columbia, Mo *Lecturer in Physiology, Stanford University, Professor Emeritus of Physiology and Pharmacology, University of Missouri* (1, 1900, 2, 1919, 3, 1909)
- Greene, Harry S N**, M D, C M Department of Pathology, Yale University School of Medicine, New Haven, Conn *Professor of Pathology* (4, 1937)
- Greene, James Alexander**, M D Baylor University, College of Medicine, Buffalo Drive, Houston, Texas *Professor and Chairman of the Department of Internal Medicine and Dean of the Clinical Faculty* (1, 1939)
- Greene, Ronald R**, M S, M D Northwestern University Medical School, 303 E Chicago Ave, Chicago, Ill *Instructor in Physiology, Instructor in Obstetrics and Gynecology* (1, 1941)
- Greengard, Harry**, Ph D, M D Northwestern University Medical School, 303 E Chicago Ave, Chicago, Ill *Assistant Professor of Physiology* (1, 1939)
- Greenstein, Jesse P**, Ph D National Cancer Institute, Bethesda, Md *Principal Biochemist* (2, 1935)
- Greenwald, Isidor**, Ph D 477 First Ave, New York City *Associate Professor of Chemistry, New York University College of Medicine* (2, 1912, 5, 1933)
- Greep, Roy O**, Ph D Harvard School of Dental Medicine, 188 Longwood Ave, Boston 15, Mass

- Assistant Professor of Dental Science (Dental Medicine), Teaching Fellow in Anatomy (Medical School) (1, 1910)*
- Greer, C M, M S Vanderbilt University School of Medicine, Nashville, Tenn *Research Associate in Pharmacology (3, 1938)*
- Gregersen, Magnus I, A M, Ph D College of Physicians and Surgeons, Columbia University, 630 W 168th St, New York City *Professor of Physiology (1, 1933)*
- Gregg, Donald Eaton M S, Ph D, M D University of Rochester Medical School, 260 Crittenden Blvd, Rochester 7, N Y (1, 1933)
- Gregory, Raymond L, Ph D, M D University of Texas School of Medicine, 1419-21th St, Galveston *Professor of Medicine (1, 1945)*
- Greig, Margaret F, B A, M A, Ph D Vanderbilt Univ School of Medicine, Nashville 4, Tenn *Assistant Professor in Pharmacology (3, 1946)*
- Greisheimer, Esther M, Ph D, M D Temple University Medical School, 3400 N Broad St, Philadelphia, Pa *Professor of Physiology (1, 1925)*
- Grenell, Robert G, Ph D Section of Neuroanatomy, Yale University School of Med, New Haven 11, Conn *Research Assistant (rank of Instructor), Laboratory of Physiology (1, 1945)*
- Griffin, Angus, Ph D Department of Bacteriology, George Washington University School of Medicine, 1335 H St, N W, Washington, D C *Assistant Professor of Bacteriology (6, 1940)*
- Griffith, Fred R, Jr, M A, Ph D 24 High St, Buffalo, N Y *Professor of Physiology, University of Buffalo Medical School (1, 1923, 5, 1933)*
- Griffith, Wendell H, M S, Ph D St Louis Univ School of Medicine, St Louis 4, Mo *Professor of Biological Chemistry (2, 1923, 5, 1934)*
- Grimson, Keith S, M D Duke University School of Medicine, Durham, N C *Associate Professor of Surgery (1, 1943)*
- Grindlay, John H, M D Mayo Clinic, Rochester, Minn (1, 1945)
- Groat, Richard A, Ph D Bowman Gray School of Medicine, Winston Salem 7, N C (1, 1945)
- Groat, William A, M D 713 E Genesee St, Syracuse, N Y *Professor of Clinical Pathology, Syracuse University College of Medicine (6, 1917)*
- Grodins, Fred S, M D School of Aviation Medicine, Randolph Field, Texas *Captain, M C (1, 1945)*
- Grollman, Arthur, M D, Ph D Southwestern Medical College, 2211 Oak Lawn Ave, Dallas, Texas *Research Professor of Medicine and Associate Professor of Biochemistry (1, 1928, 3, 1933)*
- Gross, Erwin G, Ph D, M D Medical Laboratories, State University of Iowa, Iowa City *Professor of Pharmacology (1, 1927, 2, 1923, 3, 1927)*
- Gross, Robert E, M D Harvard Medical School, 300 Longwood Ave, Boston, Mass *Assistant Professor of Surgery (4, 1910)*
- Grossman, Morton Irvin, M S, Ph D, M D, Dept of Physiology, Northwestern Univ Med School, 303 E Chicago Ave, Chicago, Ill *Instructor in Physiology (1, 1946)*
- Gruber, Charles M, A M, M D, Ph D Jefferson Medical College, 1025 Walnut St, Philadelphia, Pa *Professor of Pharmacology (1, 1914, 3, 1919)*
- Gruhitz, Oswald M, M D Research Laboratories, Parke, Davis & Co, Detroit, Mich *Research in Pathology and Pharmacology (4, 1928)*
- Grundfest, Harry, A M, Ph D Columbia Univ P and S, 630 West 168th St, New York 32, N Y *Associate in Neurology (1, 1932)*
- Gudernatsch, F, Ph D Graduate School, New York University, Washington Square E, New York City *Visiting Professor (1, 1930)*
- Guerrant, N B, M S, Ph D Pennsylvania State College, State College *Professor of Biological Chemistry (2, 1934, 5, 1933)*
- Guest, George Martin, M S, M D The Children's Hospital, Research Foundation, Elland and Bethesda Aves, Cincinnati, O *Fellow of the Children's Hospital Research Foundation, Associate Professor of Pediatrics, University of Cincinnati, College of Medicine and Graduate School (2, 1933)*
- Guest, Maurice Mason, Ph D Dept of Physiology, Wayne Univ, College of Medicine, Detroit 26, Mich *Assistant Professor of Physiology (1, 1946)*
- Gulick, Addison, A M, Ph D 308 Westmount Ave, Columbia, Mo *Professor of Physiological Chemistry, University of Missouri (1, 1915, 5, 1933)*
- Gunn, Francis D, M D University of Utah, School of Medicine, Salt Lake City *Professor of Pathology (4, 1938)*
- Gunsalus, Irwin C, Ph D Laboratory of Bacteriology, Cornell Univ, Ithaca, N Y *Associate Professor of Bacteriology (2, 1946)*
- Gurin, S, M S, Ph D University of Pennsylvania School of Medicine, Philadelphia *Assistant Professor in Physiological Chemistry (2, 1938)*
- Gustavson, Reuben G, Ph D University of Chicago, Chicago 37, Ill *Vice President and Dean of Faculties (2, 1927)*
- Gustus, Edwin L, M Sc, Ph D 5321 S Cornell Ave, Chicago 15, Ill (2, 1934)
- Guthrie, Charles Claude, M D, Ph D, Sc D University of Pittsburgh Medical School, Pittsburgh, Pa *Professor of Physiology and Pharmacology (1, 1905, 3, 1909)*

- Guttman, Rita M, M A, Ph D, 263 Eastern Parkway, Brooklyn 16, N Y, *Instructor in Physiology* (1, 1946)
- Gyorgy, Paul, M D 3400 Spruce St, Philadelphia 4, Pa *Clinical Professor of Pediatrics, University of Pennsylvania School of Medicine* (2, 1938, 5, 1939)
- Haag, Harvey B, M D Medical College of Virginia, Richmond *Professor of Pharmacology* (3, 1934)
- Haag, J R, Ph D Oregon Agricultural Experiment Station, Corvallis *Chemist* (5, 1941)
- Haas, Erwin, Ph D Institute of Pathology, Western Reserve Univ, Cleveland, Ohio *Assistant Professor in Experimental Pathology* (2, 1946)
- Haberman, Sol, M A, Ph D Wm Buchanan Blood, Plasma and Serum Center, Baylor Hospital, Dallas, Texas *Chief of Bacteriology and Serology Services* (6, 1944)
- Hadidian, Zareh, Ph D Worcester State Hospital, Worcester, Mass *Physiologist, Memorial Foundation for Neuroendocrine Research* (1, 1945)
- Hadley, Philip Bardwell, Ph D Institute of Pathology, Western Pennsylvania Hospital, Pittsburgh *Chief of Bacteriological Service and Research Bacteriologist* (4, 1927)
- Hafkesbring, H Roberta, Ph D Woman's Medical College of Pennsylvania, East Falls, Philadelphia *Professor of Physiology* (1, 1931)
- Haggard, Howard W, M D 4 Hillhouse Ave, New Haven, Conn *Director of the Laboratory of Applied Physiology, Yale University* (1, 1919, 2, 1920)
- Hahn, Paul F, Ph D Vanderbilt University School of Medicine, Nashville, Tenn *Associate Professor of Biochemistry* (4, 1939, 1, 1946)
- Haig, Charles, M A, Ph D New York Medical College, Flower and Fifth Avenue Hospital, Fifth Ave at 105th St, New York City *Assistant Professor of Physiology* (1, 1942)
- Haist, Reginald E, M A, M D, Ph D University of Toronto, Toronto, Ontario, Canada *Associate Professor of Physiology* (1, 1943)
- Haldi, John, A M, Ph D Emory University, Emory University, Ga (1, 1928)
- Hale, Worth, M D Harvard Medical School, Boston, Mass *Associate Professor of Pharmacology* (1, 1908, 3, 1908)
- Hale, Wm M, M D The State University of Iowa College of Medicine, Iowa City *Professor of Bacteriology* (4, 1941, 6, 1935)
- Hall, F G, M A, Ph D Duke Univ School of Medicine, Dept of Physiology and Pharmacology, Durham, N C (1, 1937)
- Hall, George Edward, M D, Ph D University of Western Ontario, Ottawa Ave and Waterloo St, London, Canada *Dean of the Faculty of Medicine* (1, 1938)
- Hall, Victor E, M A, M D Department of Physiology, Stanford University, Calif *Professor of Physiology* (1, 1931)
- Hallenbeck, George Aaron, Ph D, M D Aero Med Lab, Eng Div, Air Tech Serv Command, Wright Field, Dayton, Ohio *Chief, Acceleration Unit* (1, 1916)
- Halliday, Nellie, Ph D University of California Hospital, San Francisco 22, Calif (5, 1933)
- Halpert, BCl, M D University of Oklahoma School of Medicine, Oklahoma City *Director of Laboratories and Professor of Clinical Pathology* (4, 1936)
- Halsey, John T, M D P O Box 261, Waveland, Miss *Professor Emeritus of Pharmacology, Tulane University of Louisiana* (3, 1929)
- Halstead, Ward C, M A, Ph D Dept of Medicine, University of Chicago, Chicago, Ill *Associate Professor Experimental Psychology, Division of Psychiatry* (1, 1912)
- Ham, Arthur W, M B University of Toronto, Toronto 5, Canada *Professor of Anatomy, in charge of Histology* (4, 1939)
- Hambourger, Walter E, Ph D, M D G D Searle & Co, P O Box 5110, Chicago, Ill *Chief Pharmacologist* (3, 1934)
- Hamilton, Bengt L K, M D U S Marine Hospital, Staten Island, N Y *Senior Surgeon, U S Public Health Service R (Serving overseas)* (2, 1925)
- Hamilton, James B, Ph D Department of Anatomy, Long Island College of Med, 350 Henry Street, Brooklyn 2, N Y (1, 1938)
- Hamilton, Paul B, M A, Ph D Alfred I Du Pont Institute, Nemours Foundation, Wilmington, Del *Chief of Biochemistry* (2, 1946)
- Hamilton, Tom S, M S, Ph D 551 Old Agricultural Building, Urbana, Ill *Professor and Chief of Animal Nutrition, University of Illinois* (2, 1937, 5, 1938)
- Hamilton, W F, Ph D University of Georgia School of Medicine, Augusta *Professor of Physiology and Pharmacology* (1, 1924)
- Hammett, Frederick S, M S, A M, Ph D 493 Commercial St, Provincetown, Mass *Scientific Director, Lankenau Hospital Research Institute, Philadelphia, Pa* (1, 1920, 2, 1917)
- Hammon, William McD, M D, M P H, Dr P H 254 Nawona St, San Francisco, Calif *Acting Dean and Professor of Epidemiology, Univ of Calif School of Public Health, and Professor of Epidemiology, George Williams Hooper Foundation* (4, 1944)
- Hampel, C W, Ph D New York University College of Medicine, New York N Y *Visiting Professor of Physiology* (1, 1936)
- Handler, Philip, M S, Ph D Duke University School of Medicine, Durham, N C *Assistant Professor of Biochemistry and Nutrition* (2, 1944, 5, 1946)

- Handley, Carroll A, Ph D Baylor Univ College of Medicine, Houston 1, Texas *Professor of Physiology and Pharmacology* (3, 1912)
- Haney, Hance F, Ph D, M D University of Oregon Medical School, Portland *Professor of Physiology and Head of the Department* (1, 1939)
- Hanger, Franklin, M D College of Physicians and Surgeons, 630 W 168th St, New York City *Associate Professor of Medicine, Columbia University* (6, 1930)
- Hanke, Martin E, Ph D University of Chicago, Chicago, Ill *Associate Professor of Biochemistry* (2, 1925)
- Hanke, Milton Theo, Ph D 7550 S Green St, Chicago, Ill *Research Consultant, Biochemistry and Nutrition* (2, 1919)
- Hanks, John H, Ph D Culhon, Palawan, Philippine Islands (6, 1935)
- Hansen, Arild E, M D University of Texas Medical School, Galveston *Professor of Pediatrics and Chairman of the Department, Director of the University of Texas Child Health Program* (4, 1941, 5, 1942)
- Hanzal, Ramon F, M A, Ph D Killian Research Laboratories, 49 W 45th St, New York City *Biochemist* (2, 1935)
- Hanzlik Paul J, M D School of Medicine, Stanford University, Sacramento and Webster Sts, San Francisco, Calif *Professor of Pharmacology* (1, 1912, 3, 1912)
- Hardy, James Daniel, A M, Ph D Russell Sage Institute of Pathology, 525 E 68th St, New York City *Research Associate* (1, 1939)
- Hardy, Mary, D Sc The Brearley School, 610 E 83rd St, New York City *Teacher of Science* (1, 1933)
- Hare, Kendrick, Ph D 1300 York Ave, New York, N Y (1, 1938)
- Harger, R N, M A, Ph D Indiana University School of Medicine, Indianapolis *Professor of Biochemistry and Toxicology* (2, 1938)
- Harkins, Henry Nelson, M S, Ph D, M D Johns Hopkins Hospital, Baltimore, Md *Associate Professor of Surgery, Johns Hopkins University Medical School* (1, 1942)
- Harmon, Paul M, A M, Ph D Indiana University, Bloomington *Professor of Physiology* (1, 1930)
- Harne, O G University of Maryland School of Medicine, Baltimore *Associate Professor of Histology* (1, 1935)
- Harned, Ben King, M S, Ph D Lederle Laboratories, Pearl River, N Y *Associate Head, Division of Pharmacology* (2, 1931, 3, 1941)
- Harris, Albert H, M D, N Y State Dept of Health, Division of Laboratories and Research, New Scotland Ave, Albany 1, N Y *Associate Bacteriologist* (6, 1937)
- Harris, Albert Sidney, Ph D Western Reserve University School of Medicine, Cleveland, O *Assistant Professor of Physiology* (1, 1939)
- Harris, Milton, Ph D 1216 Taylor St, N W, Washington 11, D C *Director of Research, Milton Harris Associates* (2, 1939)
- Harris, Philip L, M S, Ph D Distillation Products, Inc, 755 Ridge Road W, Rochester 13, N Y *Head of Biochemistry Research Department, and Instructor in Physiology, University of Rochester Medical School* (5, 1915, 2, 1946)
- Harris, Robert S Massachusetts Institute of Technology, Cambridge *Professor of Nutritional Biochemistry* (5, 1911)
- Harris, T N, M D, 2222 N 53rd St, Philadelphia 31, Pa *Associate in Pediatrics, Univ of Pennsylvania* (6, 1946)
- Harris, William H, M D Tulane University School of Medicine, New Orleans, La *Assistant Professor of Pathology and Bacteriology* (4, 1925)
- Harrison, Frank, M S, Ph D University of Tennessee College of Medicine, Memphis *Assistant Professor in Anatomy* (1, 1941)
- Harrison, James A, Ph D Temple Univ, Philadelphia 22, Pa *Professor of Biology* (6, 1946)
- Harrison, Ross Granville, M D, Ph D, Sc D Osborn Zoological Laboratory, New Haven, Conn *Sterling Professor of Biology, Emeritus, Yale University, Chairman of the National Research Council, Member of the National Academy of Sciences* (1, 1906)
- Harrison, R Wendell, M D, Ph D 950 East 59th St, Chicago 37, Ill *Professor of Bacteriology, Dean, Division of Biological Sciences, Univ of Chicago* (6, 1934)
- Harrow, Benjamin, M A, Ph D College of the City of New York, Convent Ave and 139th St, New York City *Professor of Chemistry* (2, 1927)
- Hart, E B, B S Agricultural College, Madison, Wis *Professor of Biochemistry, University of Wisconsin* (2, 1910, 5, 1933)
- Hart, E Ross, M S, Ph D Jefferson Medical College, 1025 Walnut St, Philadelphia, Pa *Assistant Professor of Pharmacology* (3, 1944)
- Hart, William M, Ph D Temple Medical School, Broad and Ontario Sts, Philadelphia 40, Pa *Assistant Professor of Physiological Chemistry* (1, 1945)
- Hartley, Geo, Jr, M A, Ph D, M D Boston Univ School of Medicine, 80 E Concord St, Boston, Mass *Assistant Professor of Pathology* (6, 1941)
- Hartline, H K, M D Johnson Foundation University of Pennsylvania, Philadelphia, Pa, *Assistant Professor of Biophysics* (1, 1929)
- Hartman, Carl G, A M, Ph D Department of Zoology, University of Illinois, Urbana *Professor of Zoology and Head of the Department,*

- Member, *National Academy of Sciences* (1, 1921)
- Hartman, Frank Alexander, A.M., Ph.D. Department of Physiology, Ohio State University, Columbus *Professor of Physiology and Chairman of the Department* (1, 1916)
- Hartman, F. W., M.D. Henry Ford Hospital, Detroit, Mich. *Pathologist* (4, 1927)
- Hartmann, Alexis F., M.S., M.D. 500 S. Kingshighway, St. Louis, Mo. *Professor of Pediatrics, Washington University School of Medicine* (2, 1932)
- Harvey, A. McGhee, A.B., M.D. Johns Hopkins Hospital, Baltimore 5, Md. *Professor of Medicine, Johns Hopkins Univ. Medical School, Physician-in-chief, Johns Hopkins Hospital* (1, 1916, 3, 1946)
- Harvey, E. Newton, Ph.D. Guyot Hall, Princeton, N.J. *Henry Fairfield Osborn Professor of Biology, Princeton University, Member, National Academy of Sciences* (1, 1914, 2, 1916)
- Hass, George, M.D. Presbyterian Hospital of Chicago, 1753 W. Congress St., Chicago 12, Ill. *Professor of Pathology, Univ. of Illinois College of Medicine, Chairman of Dept. of Pathology, Presbyterian Hospital of Chicago* (4, 1939)
- Hassid, William Z., M.S., Ph.D. Division of Plant Nutrition, Univ. of California, Berkeley, Calif. *Associate Professor of Plant Nutrition* (2, 1946)
- Hastings, A. Baird, Ph.D., Sc.D. Harvard Medical School, Boston, Mass. *Hamilton Kuhn Professor of Biological Chemistry, Member, National Academy of Sciences* (1, 1927, 2, 1921, 5, 1940)
- Haterius, Hans O., Ph.D. Boston University School of Medicine, 80 E. Concord St., Boston 18, Mass. *Professor of Physiology* (1, 1936)
- Hathaway, Milcent L., M.A., Ph.D. Bureau of Human Nutrition and Home Economics, (Food and Nutrition Division), Agricultural Research Administration, Washington 25, D.C. (5, 1945)
- Hauck, Hazel M., Ph.D. Cornell University, Ithaca, N.Y. *Professor of Home Economics* (5, 1941)
- Hauge, Siegfried M., Ph.D. Purdue University Agricultural Experiment Station, Lafayette, Ind. *Research Associate in Biochemistry* (5, 1933)
- Haurv, Victor G., M.B., M.D. 1428 S. Willow St., Ottawa, Kansas (3, 1939)
- Haven, Frances L., M.A., Ph.D. University of Rochester School of Medicine and Dentistry, 260 Crittenden Blvd., Rochester, N.Y. *Associate in Biochemistry* (2, 1941)
- Hawk, Philip B., M.S., Ph.D. 750 W. 50th St., Miami Beach, Fla. *President, Food Research Laboratories, Inc.* (1, 1903, 2, 1906)
- Hawkins, J. E., Jr., B.A. (Oxon), Ph.D. Bowman Gray School of Medicine, Winston-Salem, N.C. *Assistant Professor of Physiology* (1, 1913)
- Hawkins, William Bruce, M.D. University of Rochester School of Medicine and Dentistry, 260 Crittenden Blvd., Rochester, N.Y. *Associate Professor of Pathology* (4, 1933)
- Hawks, Jean E. Division of Home Economics, Michigan State College, East Lansing. *Associate Professor of Nutrition* (5, 1914)
- Hawley, Estelle E., Ph.D. Medical School, University of Rochester, Rochester, N.Y. *Research Fellow in Pediatrics* (5, 1935)
- Hay, Eleanor Clarke, Ph.D. McGill University, Montreal, Canada (1, 1915)
- Hayman, J. M., Jr., M.D. Lakeside Hospital, Cleveland, O. *Professor of Clinical Medicine and Therapeutics, Western Reserve University* (1, 1928, 3, 1932)
- Haynes, Florence W., M.A., Ph.D. Harvard Medical School, 25 Shattuck St., Boston, Mass. *Research Fellow in Medicine* (1, 1937)
- Hays, Edwin Everett, M.S., Ph.D. Dept. of Biochemistry, College of Medicine, Univ. of Vermont, Burlington, Vt. *Assistant Professor of Biochemistry* (2, 1946)
- Haythorn, Samuel R., M.D. Allegheny General Hospital, 320 E. North Ave., Pittsburgh, Pa. *Director of William H. Singer Memorial Laboratory* (4, 1925)
- Haywood, Charlotte, A.M., Ph.D. Mount Holyoke College, South Hadley, Mass. *Professor of Physiology* (1, 1939)
- Hazen, Elizabeth L., M.A., Ph.D. New York State Department of Health Laboratories, 339 E. 25th St., New York City. *Senior Bacteriologist* (6, 1931)
- Hazelton, Lloyd W., Ph.D. Box 333, Falls Church, Va. (3, 1944)
- Heard, R. D. H., M.A., Ph.D. Dept. of Biochemistry, McGill Univ., Montreal, Canada. *Associate Professor of Biochemistry* (2, 1938)
- Hecht, Selig, Ph.D. Columbia University, New York City. *Professor of Biophysics, Member, National Academy of Sciences* (1, 1920)
- Hechter, Oscar M., Ph.D. Worcester Foundation Experiment Biol., 222 Maple Ave., Shrewsbury, Mass. (1, 1945)
- Heft, Hattie L., Ph.D. Teachers College, Columbia University, New York City. *Assistant Professor of Physiological Chemistry* (2, 1927)
- Hegnauer, Albert H., Ph.D. Syracuse University, Syracuse, N.Y. *Assistant Professor of Physiology* (1, 1937)
- Hegsted, David Mark, M.S., Ph.D. Schools of Medicine & Public Health, Harvard University, 25 Shattuck St., Boston, Mass. *Assistant Professor of Nutrition* (5, 1944)

- Heidelberger, Michael, Ph D , M A 620 W 168th St , New York City *Professor of Biological Chemistry, Columbia University, Chemist to the Medical Service, Presbyterian Hospital* (2, 1927, 6, 1935)
- Heilbrunn, Lewis Victor, Ph D University of Pennsylvania, Philadelphia *Professor of Zoology* (1, 1930)
- Heim, J William, Ph D Aero Medical Laboratory, Army Air Forces, Wright Field, Dayton, O *Principal Research Physiologist, Assistant in Physiology, Harvard School of Public Health* (1, 1936)
- Heinbecker, Peter, M D Washington University Medical School, St Louis, Mo *Associate Professor of Clinical Surgery* (1, 1930)
- Heiff, O M , M S , Ph D New York University, University Heights, New York City *Associate Professor of Biology* (1, 1932)
- Hellbaum, Arthur A , M A , Ph D , M D University of Oklahoma School of Medicine, Oklahoma City *Professor of Pharmacology* (1, 1937, 3, 1945)
- Hellebrandt, Frances Anna, M D Medical College of Virginia, Richmond *Professor of Physical Medicine* (1, 1933)
- Heller, Carl G , M D , Ph D University of Oregon Medical School, Portland 1 *Associate Professor of Physiology and Medicine* (1, 1945)
- Heller, Victor G , Ph D Oklahoma A & M College, Stillwater *Head of the Department of Agricultural Chemistry Research* (2, 1935, 5, 1935)
- Hellerman, Leslie, Ph D Johns Hopkins University School of Medicine, 710 N Washington St , Baltimore, Md *Assistant Professor Physiological Chemistry* (2, 1935)
- Helmer, Oscar Marvin, M S , Ph D Lilly Laboratory for Clinical Research, The Indianapolis City Hospital, Indianapolis, Ind *Head of Department of Physiological Chemistry, Research Associate in the Department of Medicine, Indiana University School of Medicine* (2, 1935)
- Hemingway, Allan, Ph D 241 Cecil St , S E , Minneapolis *Associate Professor of Physiology, University of Minnesota* (1, 1933)
- Hendrix, Byron M , Ph D School of Medicine, University of Texas, Galveston *Professor of Biochemistry* (2, 1920)
- Hendrix, James Paisley, B S , M A , M D Duke Hospital, Durham, N C *Associate in Medicine (in charge of Therapeutics), Associate in Physiology and Pharmacology, Duke University School of Medicine* (3, 1942)
- Hendry, Jessie L , M A Division of Laboratories and Research, New York State Department of Health, New Scotland Ave , Albany *Senior Bacteriologist* (6, 1938)
- Henle, Werner, M D 1710 Bainbridge St , Philadelphia 46, Pa *Associate Professor of Virology in Pediatrics* (6, 1938)
- Henschel, Austin F , Ph D University of Minnesota Minneapolis *Assistant Professor of Physiological Hygiene* (1, 1914)
- Hepburn, Joseph Samuel, A M , M S , Ph D , M D Chem D 235 N 15th St , Philadelphia 2, Pa *Professor of Chemistry and Research Associate in Gastro Enterology, Hahnemann Medical College and Hospital* (2, 1915)
- Hepler, Opal E , Ph D , M D Northwestern University Medical School, 303 E Chicago Ave , Chicago, Ill *Assistant Professor of Pathology* (4, 1939)
- Herbst, R M , Ph D 39 Knollwood Road, Short Hills, N J *Director of Research, E Bilhuber, Inc , Orange, N J* (2, 1938)
- Herrick, C Judson, Ph D 236 Morningside Drive, Grand Rapids, Mich *Professor Emeritus of Neurology, University of Chicago, Member of the National Academy of Sciences* (1, 1907)
- Herrick, Julia F , M A , Ph D P O Box 41 Asbury Park, N J (1, 1933)
- Herrin, Raymond C , Ph D , M D University of Wisconsin Medical School, Madison *Associate Professor of Physiology* (1, 1932)
- Herrington, Lovic P , M A , Ph D 290 Congress Ave , New Haven, Conn *Associate Director, John B Pierce Laboratory of Hygiene, Research Associate Professor, Dept of Public Health, Yale Medical School* (1, 1942)
- Herriott, Roger M , Ph D Rockefeller Institute for Medical Research, Princeton, N J *Associate* (2, 1940)
- Herrmann, George, Ph D , M D University of Texas, Medical Branch, Galveston *Professor of Medicine* (4, 1925)
- Hermann, Julian B , Ph B , M D 2 East 94th St , New York 28, N Y (3, 1941)
- Herrmann, Louis George, M D Cincinnati General Hospital, Cincinnati 29, O *Associate Professor of Surgery, University of Cincinnati College of Medicine, Assistant Director of Surgical Services, Cincinnati General Hospital and Children's Hospital* (4, 1933)
- Hershey, A D , Ph D Washington University School of Medicine, St Louis, Mo *Associate Professor of Bacteriology and Immunology* (6, 1942)
- Hertig, Arthur T , M D Harvard University Medical School, 221 Longwood Ave , Boston, Mass *Assistant Professor of Pathology and Assistant Professor of Obstetrics* (4, 1941)
- Hertz, Roy, Ph D , M D National Institute of Health, Bethesda 14, Md *P H Surgeon (R), Division of Physiology* (1, 1945)

- Hertz, Saul, M D** Massachusetts General Hospital, Fruit St, Boston *Research Associate, Harvard Medical School and Massachusetts Institute of Technology* (4, 1935)
- Hertzman, Alrick B, Ph D** St Louis University School of Medicine, St Louis, Mo *Professor of Physiology and Director of the Department* (1, 1925)
- Herwick, Robert P, Ph D, M D, LL B U S** Food and Drug Administration, Washington, D C *Chief, Drug Division, Associate Prof Pharmacology, Georgetown Medical School, Adjunct Clinical Professor Medicine (Therapeutics) George Washington Medical School* (3, 1938)
- Hess, Charles L, M S, M D** 308 Davidson Bldg, Bay City, Mich (1, 1916)
- Hess, Charles C, Ph D** Georgetown Medical School, 37 and Reservoir Rd, N W Washington, D C *Professor of Physiological Chemistry* (2, 1935)
- Hetherington, Albert W, M S, Ph D** Northwestern University Medical School, 303 E Chicago Ave, Chicago, Ill *Instructor in Neurology* (1, 1943)
- Hewitt, Earl Albon, M S, Ph D** Iowa State College, Ames *Associate Professor of Veterinary Physiology* (1, 1932)
- Hewitt, Julia A W, B A** 2631 Central Ave, N E, Minneapolis 13, Minn (6, 1921)
- Heyroth, Francis F, M D, Ph D** Kettering Laboratory, College of Medicine, University of Cincinnati, Cincinnati, O *Assistant Professor of Applied Physiology* (2, 1935)
- Hiatt, Edwin P, M A, Ph D** North Carolina University School of Medicine, Chapel Hill *Associate Professor of Physiology* (1, 1942)
- Hickman, Kenneth C D, Ph D** Distillation Products, Inc, 755 Ridge Road W, Rochester, N Y *Vice-President and Director of Research* (2, 1944)
- Higgins, Harold Leonard, M D** 322 Franklin, Newton, Mass *Assistant Professor of Pediatrics, Harvard University* (1, 1914, 5, 1933)
- Hill, Edgar S, M S, Ph D** Washington University, College of Dentistry, St Louis, Mo *Associate Professor of Biological Chemistry and Physiology* (2, 1936)
- Hill, Robert M, M S, Ph D** 4200 E 9th Ave, Denver, Colo *Associate Professor of Biochemistry, University of Colorado Medical School* (2, 1933)
- Hill, Samuel E, M A, Ph D** 18 Collins Ave, Troy, N Y *Research Worker, The Behr-Manning Corp* (1, 1934)
- Hiller, Alma, Ph D** Rockefeller Institute for Medical Research, 66th St and York Ave, New York City *Associate* (2, 1929)
- Himmelsbach, C. K, M D** Suite 2308, 188 West Randolph, Chicago, Ill (3, 1938)
- Himwich, Harold E, M D** Fallston, Md *Chief, Clinical Research Branch, Army Chemical Center, Edgewood Arsenal, Maryland* (1, 1925, 5, 1933)
- Hines, Harry M, M S, Ph D** The State University of Iowa, Iowa City *Professor of Physiology* (1, 1928)
- Hines, Marion, Ph D** Johns Hopkins Medical School, Baltimore, Md *Associate Professor of Anatomy* (1, 1932)
- Hinrichs, Marie, Ph D, M D** Southern Illinois Normal University, Carbondale *Professor of Physiology, Director of Student Health Service* (1, 1925)
- Hinsey, Joseph C, M S, Ph D** Cornell University Medical College, 1300 York Ave, New York City *Professor of Anatomy and Dean of the Medical College* (1, 1929)
- Hirschmann, Hans, M D, Ph D** Lakeside Hospital, Cleveland, Ohio *Assistant Professor of Biochemistry, Department of Medicine, Western Reserve University* (2, 1916)
- Hisaw, Frederick L, A M, Ph D** The Biological Laboratories, Harvard University, Cambridge Mass *Professor of Zoology* (1, 1932)
- Hitchcock, David I, Ph D** 333 Cedar St, New Haven, Conn *Associate Professor of Physiology, Yale University* (2, 1930)
- Hitchcock, Fred A, M Sc, Ph D** Ohio State University, Columbus *Professor of Physiology* (1, 1927, 5, 1933)
- Hitchcock, Philip, A B, M S, Ph D** Department of Physiology and Pharmacology, Medical College of Alabama, Birmingham 5, Ala *Assistant Professor of Physiology and Pharmacology* (3, 1946)
- Hitchings, George H, M S, Ph D** 50 Primrose Ave, Tuckahoe 7, N Y *Biochemist, Wellcome Research Laboratories* (2, 1942)
- Hjort, Axel M, M D, Ph D P O Box 281, 14 Fern Way, Scarsdale, N Y** *Adjunct Physician, Grasslands Hospital, Valhalla, N Y* (2, 1925)
- Hoagland, Hudson, M S, Ph D** Worcester State Hospital, Worcester, Mass (1, 1932)
- Hobby, Gladys L, A B, M A, Ph D** 11 Bartlett St, Brooklyn 6, N Y *Bacteriologist, Chas Pfizer & Co* (6, 1946)
- Hober, Rudolf** University of Pennsylvania Medical School, Philadelphia *Visiting Professor of Physiology* (1, 1936)
- Hodes, Robert, Ph D** Johnson Foundation, University of Pennsylvania, Philadelphia *Associate in Biophysics* (1, 1941)
- Hodge, Harold C, Ph D** University of Rochester School of Medicine and Dentistry, Rochester, N Y *Associate Professor of Biochemistry and Pharmacology* (2, 1937)
- Hoefler, Paul F A, Ph D, M D** Neurological Institute of New York, 710 W 168th St, New York 32, N Y *Associate Professor of Neurology* (1, 1945)

- Hoff, Ebbe Curtis, M A , Ph D Department of Physiology, Yale University School of Medicine, 333 Cedar St, New Haven, Conn (1, 1933)
- Hoff, Hebbel E, M A , Ph D McGill University, Montreal, Quebec, Canada Professor of Physiology (1, 1933)
- Hoffman, Olive, M S , Ph D Presbyterian Hospital, 51 N 39th St, Philadelphia, Pa (1, 1935)
- Hoffman, William Samuel, Ph D , M D 629 S Wood St, Chicago, Ill Acting Director of Laboratories and Acting Director of the Hektoen Institute for Medical Research, Cook County Hospital (2, 1935)
- Hogan, Albert G , M A , Ph D 105 Schweitzer Hall, Columbia, Mo Professor of Animal Nutrition, University of Missouri (2, 1916, 5, 1933)
- Hogness, Thorfin R , Ch E , Ph D Department of Chemistry, University of Chicago, Chicago, Ill Professor of Chemistry (2, 1941)
- Holch, Harald G O , Ph D College of Pharmacy, University of Nebraska, Lincoln Associate Professor of Pharmacology (1, 1935, 3, 1938)
- Hollander, Franklin, Ph D Mount Sinai Hospital, Fifth Ave and 100th St, New York City Associate in Physiology, Head, Gastro-Enterology Research Laboratory (1, 1942, 2, 1932)
- Helm, August, Sc D E R Squibb & Sons, New Brunswick, N J Head, Bacteriology Developing Laboratories (6, 1946)
- Holman, Russell Lowell, M D Louisiana State University School of Medicine, New Orleans, La Professor of Pathology (4, 1940)
- Holmes, Arthur Dunham, Ph D Massachusetts State College, Amherst Research Professor of Chemistry (2, 1931, 5, 1933)
- Holmes, Julia O , M S , Ph D Massachusetts State College, Amherst Research Professor of Nutrition (2, 1942, 5, 1936)
- Holt, Joseph Paynter, M S , M D , Ph D Standard Oil Co, Room 2400, 30 Rockefeller Plaza, New York 20, N Y Director of Medical Research (1, 1942)
- Holt, L Emmett, Jr, M D 477 First Ave, New York 16, N Y Professor of Pediatrics, New York University College of Medicine (2, 1930, 5, 1946)
- Hoobler, Icie Macy, M S , Ph D , Sc D 660 Frederick St, Detroit, Mich Director, Research Laboratory Children's Fund of Michigan (2, 1925, 5, 1933)
- Hooker, Davenport, M A , Ph D University of Pittsburgh School of Medicine, Pittsburgh, Pa Professor of Anatomy (1, 1920)
- Hooker, Sanford B, A M , M D 80 E Concord St, Boston, Mass Member, Evans Memorial (6, 1918)
- Hoover, Sam R, M A , Ph D 7815 Linden Rd, Philadelphia 18, Pa Senior Chemist Eastern Regional Research Laboratory, U S Department of Agriculture (2, 1946)
- Hoppert, C A , Ph D Michigan State College, Box 626, East Lansing Professor of Biological Chemistry (5, 1935)
- Hopps, Howard C, M D Department of Pathology, University of Oklahoma School of Medicine, 801 E 13th St, Oklahoma City, Okla Professor of Pathology and Chairman of Dept (6, 1946)
- Horowitz, Norman H, Ph D Biology Department, California Institute of Technology, Pasadena, Calif Senior Research Fellow (2, 1946)
- Horsfall, Frank L, Jr, M D , C M Rockefeller Institute, 66th St and York Ave, New York City Member (6, 1937)
- Horvath, Steven M, M A , Ph D Dept of Physical Medicine, Hospital of the Univ of Pennsylvania, Philadelphia, Pa (1, 1943)
- Horwitt, M K, Ph D Biochemical Research Laboratory, Elgin State Hospital, Elgin, Ill Director, Biochemical Research Laboratory, Assistant Professor, Physiological Chemistry, University of Illinois School of Medicine (2, 1941)
- Hoskins, R G, Ph D , M D Harvard Medical School, Boston, Mass Research Associate in Physiology, Harvard University, Director of Research, Memorial Foundation for Neuroendocrine Research (1, 1911)
- Hotchkiss, Rollin D, Ph D The Rockefeller Institute for Medical Research, 66th St and York Ave, New York City Associate (2, 1941)
- Hove, Edwin L, M S , Ph D Distillation Products, Inc, 755 Ridge Road, West, Rochester 13, N Y Research Biochemist (5, 1946)
- Howard, Evelyn, A M , Ph D Johns Hopkins School of Medicine, Baltimore, Md Instructor in Physiology (1, 1933)
- Howard, John Eager, A B , M D Johns Hopkins Hospital, Baltimore 5, Md Assistant Professor of Medicine (1, 1946)
- Howard, Marion D, M D New Haven Hospital, New Haven, Conn Assistant Professor of Medicine, Yale School of Medicine, Associate Physician, New Haven Hospital and New Haven Dispensary (4, 1939, 6, 1937)
- Howe, Paul E, A M , Ph D Bureau of Animal Industry, U S Dept of Agriculture, Washington 25, D C Colonel, Sanitary Corps, Nutrition Consultant, Public Health and Welfare, S C 4 P, APO 500, c/o P M, San Francisco, Cal, On leave as Chief, Animal Nutrition Division, and Assistant Chief, Bureau of Animal Industry, U S Department of Agriculture (1, 1913, 2, 1909, 5, 1933)
- Howe, Percy R, M D , D D S Harvard Medical School, Boston, Mass Director Forsyth Dental Infirmary, Professor Dental Sciences, Instructor in Pathology (5, 1935)

- Howell, Katherine M**, M D Michael Reese Hospital, 2900 Ellis Ave, Chicago, Ill *Head of Departments of Bacteriology and Serology* (6, 1940)
- Howell, Stacey F**, Ph D V D Research Laboratory, U S Marine Hospital, Stapleton, Staten Island, N Y *Chemist, U S Public Health Service* (2, 1940)
- Hubbard, Roger Sanford**, A M, Ph D 100 High St, Buffalo, N Y *Biochemist, Buffalo General Hospital, Professor of Physiology, Buffalo University Medical School* (1, 1922, 2, 1920)
- Hubbell, Rebecca B**, M S, Ph D Connecticut Agricultural Experiment Station, New Haven *Assistant Biochemist* (2, 1937, 5, 1935)
- Hudack, Stephen Sylvester**, M D 180 Fort Washington Ave, New York, N Y *Associate Professor of Orthopedic Surgery, Columbia Univ* (4, 1933)
- Huddleston, Ora Leonard** M D, Ph D Fitzsimmons General Hospital, Denver, Colo *Major, MC, Instructor in Physiology, University of Colorado School of Medicine* (1, 1936)
- Hueper, Wilhelm C**, M D Warner Institute for Therapeutic Research, 113 W 18th St, New York City *Assistant Director and Principal Pathologist* (4, 1940)
- Huffman, C F**, M S, Ph D Michigan State College, East Lansing *Research Professor and Professor in Dairy Husbandry* (5, 1937)
- Huggins, Charles Brenton**, M D University of Chicago, Chicago, Ill *Professor of Surgery* (1, 1932)
- Hughes, Hettie B**, M S, Ph D The Christ Hospital, Cincinnati 19, Ohio *Research Associate* (2, 1946)
- Hughes, Joseph**, M D 111 N 49th St, Philadelphia, Pa *Assistant Professor of Experimental Neurology, Graduate School of Medicine, University of Pennsylvania, Director of Laboratory, Pennsylvania Hospital for Mental Diseases* (1, 1936)
- Hughes, Josiah Simpson**, M A, M S, Ph D Kansas State College, Manhattan *Professor of Chemistry* (2, 1931, 5, 1939)
- Hughes, Thomas P**, A M, Ph D Caixa Postal 49, Rio de Janeiro, Brazil *Member of Staff, International Health Division* (6, 1934)
- Hulpieu, Harold R**, M A, Ph D Indiana University School of Medicine, Indianapolis *Associate Professor of Pharmacology* (3, 1939)
- Hunscher, Helen A**, Ph D Western Reserve University, 2023 Adelbert Rd, Cleveland 6, O *Head of Department of Home Economics* (5, 1934)
- Hunt, Reid**, M D, Ph D, Sc D Harvard Medical School, Boston, Mass *Professor Emeritus of Pharmacology, Harvard University, Member, National Academy of Sciences* (1, 1895, 2, 1906, 3, 1908)
- Hunter, Andrew**, M A, M B, F R S C University of Toronto, Toronto, Canada *Professor of Pathological Chemistry* (2, 1908)
- Hunter, Francis Edmund, Jr**, Ph D Pharmacology Department, Washington University Medical School, St Louis 10, Mo *Assistant Professor of Pharmacology* (2, 1916)
- Hunter, George**, M A, D Sc, F R S C University of Alberta, Edmonton, Canada *Professor of Biochemistry* (2, 1921)
- Hunter, Jesse E**, M S, Ph D Allied Mills, Inc, 7500 S Adams St, Peoria, Ill *Director Biological Research* (5 1936)
- Hussey, Raymond**, M D Medical Science Center of Wayne University, 1517 Penobscot Building, Detroit 26 Mich *Dean, Prof of Preventive Medicine and Organization of School of Occupational Health* (1, 1927)
- Ingalls, Mabel S**, Ph D Salisbury Mills, Orange County, N Y (6, 1910)
- Ingle, Dwight J**, M S, Ph D The Upjohn Co Research Department, Kalamazoo, Mich *Upjohn Research Fellow* (1, 1939)
- Ingraham, Raymond Clifford**, Ph D College of Medicine, University of Illinois, 1853 W Polk St, Chicago *Assistant Professor in Physiology* (1, 1938)
- Ingram, W R**, Ph D College of Medicine, The State University of Iowa, Iowa City *Professor and Head of the Department of Anatomy* (1, 1936)
- Irvin, J Logan**, Ph D Johns Hopkins University School of Medicine, 710 N Washington St, Baltimore, Md *Assistant Professor of Physiological Chemistry* (2, 1942)
- Irving, George Washington, Jr**, M A, Ph D Bureau of Agricultural and Industrial Chemistry, Agricultural Research Center, Beltsville, Md *Principal Biochemist, Head, Biologically Active Compounds Division, U S Department of Agriculture* (2, 1946)
- Irving, Laurence**, A M, Ph D Swarthmore College, Swarthmore, Pa *Lt Col, A C Professor of Experimental Biology* (1, 1927)
- Irwin, M R**, Ph D Department of Genetics, University of Wisconsin, Madison *Professor of Genetics* (6, 1936)
- Isaacs, Raphael**, M D 104 S Michigan Ave, Suite 630, Chicago 3, Ill *Director, Department of Hematology, Michael Reese Hospital* (4, 1928)
- Isenberger, R M**, M A, M D University of Kansas School of Medicine, Kansas City *Professor of Pharmacology* (3, 1937)
- Ivy, Andrew C**, Ph D, M D 1853 West Polk St, Chicago 12, Ill *Vice-President and Distinguished Professor of Physiology, University of Illinois* (1, 1919, 5, 1933)

- Izquierdo, J Joaquin, M D National School of Medicine, Mexico City *Professor of Physiology in the National School of Medicine and the Escuela Medico Militar of Mexico* (1, 1928)
- Jackson, Dennis Emerson, A M, Ph D M D University of Cincinnati Medical School, Eden and Bethesda Aves, Cincinnati, O *Professor of Pharmacology* (1, 1910, 3, 1912)
- Jackson, Eugene L, Ph D 12 S 12th St Richmond 19 Va *Medical Director, A H Robins Co* (3 1942)
- Jackson, Richard W, Ph D Eastern Regional Research Laboratory, U S Department of Agriculture, Wyndmoor, Pa *Chief of Protein Division* (2, 1930, 5, 1933)
- Jacobs, Merkle Henry, Ph D University of Pennsylvania, Philadelphia *Professor of General Physiology, Member of the National Academy of Sciences* (1, 1919)
- Jacobs, Walter A, A M, Ph D Rockefeller Institute, 66th St and York Ave, New York City *Member, Member, National Academy of Sciences* (2, 1908, 3, 1913)
- Jacobson, Edmund, Ph D, M D Laboratory for Clinical Physiology, 55 E Washington St, Chicago, Ill (1, 1929)
- Jaffe, Henry L, M D Hospital for Joint Diseases, 1919 Madison Ave, New York City *Director of Laboratories* (4, 1925)
- Jahn, Theodore Louis, Ph D State University of Iowa, Iowa City *Associate Professor of Zoology* (1, 1944)
- Jamieson, Walter A, Sc D (hon) Eli Lilly & Company, Indianapolis, Ind *Director, Biological Division* (6, 1927)
- Jandorf, Bernard J, A M, Ph D, Medical Division, Edgewood Arsenal, Md *Acting Chief of Biochemistry Section, Lecturer in Preventive Medicine, Johns Hopkins University School of Medicine* (2, 1946)
- Jacques, L B, M A, Ph D Univ of Saskatchewan, Saskatoon, Sask, Canada *Professor of Physiology* (1, 1943)
- Jasper, Herbert H, M A, Ph D, D és Sci Montreal Neurological Institute, 3801 University St, Montreal, Que, Canada *Lecturer in Neuroelectrography and Director of Department of Electrophysiology* (1, 1940)
- Jeans, P C, M D State University of Iowa, Iowa City *Professor of Pediatrics* (5, 1937)
- Jensen, H, Ph D Des Bergers-Bismol Labs, 338 St Paul St, W Montreal, Que, Canada *Director of Research, Fellow, McGill Univ Medical School* (2, 1929)
- Jobling, James W, M D Columbia University, 630 W 168th St, New York City *Professor of Pathology* (4, 1913)
- Jochim, Kenneth E, Ph D University of Kansas, Lawrence, Kansas *Professor of Physiology* (1, 1942)
- John, J M, Ph D D Sc Vanderbilt University School of Medicine, Nashville Tenn *Associate Professor of Biochemistry* (2, 1928)
- Johnson, Frank H, A M, Ph D Princeton University, Princeton, N J *Assistant Professor, Dept of Biology* (1, 1942)
- Johnson, Joseph L, Ph D, M D School of Medicine, Howard University, Washington, D C *Professor and Head of the Department of Physiology* (1, 1934)
- Johnson, J Raymond, Ph D Long Island College of Medicine, 350 Henry St, Brooklyn, N Y *Associate Professor of Physiology and Pharmacology* (1, 1938)
- Johnson, Marvin J, M S Ph D University of Wisconsin, Madison *Associate Professor of Biochemistry* (2, 1941)
- Johnson, Robert E, M D, Ph D Army Medical Nutrition Laboratory, 1849 W Pershing Rd, Chicago 9 Ill *Director* (1, 1944, 2, 1939, 5, 1946)
- Johnson, Treat B, Ph D Amity Road, Bethany, Westville P O, Conn *Professor Emeritus, Yale University Member, National Academy of Sciences* (2, 1910)
- Johnson, Victor, Ph D, M D 5807 Dorchester Ave, Chicago, Ill *Associate Professor of Physiology, Dean of Students in the Division of Biology and the School of Medicine, University of Chicago* (1, 1933)
- Johnston, Charles G, M S, M D Wayne University College of Medicine, Detroit, Mich *Professor of Surgery* (1, 1933)
- Johnston, Margaret W, Ph D Box 452, University Hospital, Ann Arbor, Mich *Research Associate in Internal Medicine* (2, 1930, 5, 1938)
- Jolliffe, Norman, M D 39 E 75th St, New York, N Y (1, 1932)
- Jones, D Breese, Ph D Bureau of Human Nutrition and Home Economics, Agricultural Research Administration, U S Department of Agriculture, Washington, D C *Protein Chemist* (2, 1920, 5, 1935)
- Jones, James H, M S, Ph D School of Medicine, University of Pennsylvania, Philadelphia *Associate Professor of Physiological Chemistry* (2, 1928, 5, 1933)
- Jones, Kenneth K, M S, Ph D Northwestern University Medical School, 303 E Chicago Ave, Chicago, Ill *Associate Professor of Physiology and Pharmacology* (1, 1936)
- Jones, Lloyd R, M S, Ph D 1402 S Grand Blvd, St Louis, Mo *Professor and Chairman of Department of Bacteriology, St Louis University School of Medicine* (6, 1933)
- Joslin, Elliott P, M A, M D New England Deaconess Hospital, 81 Bay State Rd, Boston,

- Mass Director, George F Baker Clinic (5, 1933)
- Jukes, Thomas Hughes, Ph D Lederle Laboratories, Pearl River, N Y Head, Department of Nutrition and Physiology Research (2, 1935, 5, 1938)
- Jung, Frederic Theodore, Ph D, M D Northwestern University Medical School, Chicago, Ill Assistant Professor of Physiology and Pharmacology (1, 1930)
- Jungeblut, Claus W, M D College of Physicians and Surgeons, 630 W 168th St, New York City Professor of Bacteriology, Columbia University (4, 1929, 6, 1926)
- Kabat, Elvin A, A M, Ph D The Neurological Institute, 710 W 168th St, New York 32, N Y Assistant Professor of Bacteriology, College of Physicians and Surgeons, Columbia University and The Neurological Institute (2, 1910, 6, 1943)
- Kabat, Herman, Ph D, M D 806 Taylor St, N W, Washington, D C Consultant in Neurology, Health Department, District of Columbia (1, 1941)
- Kahn, Reuben L, Sc D, LL D University of Michigan Hospital, Ann Arbor Director of Clinical Laboratories (4, 1934, 6, 1919)
- Kalckar, Herman M, M D, Ph D Institute for Medical Physiology, University of Copenhagen, Copenhagen, Denmark Associate Professor (2, 1942)
- Kamen, Martin D, Ph D Washington University Medical School, 510 S Kingshighway, St Louis 10, Mo Associate Professor of Biochemistry, Chemist in the Mallinckrodt Institute of Radiology (2, 1946)
- Kamm, Oliver, M S, Ph D Research Laboratory, Parke, Davis & Co, Detroit, Mich Scientific Director (2, 1928)
- Karpovich, Peter V, M D, M P E Springfield College, Springfield, Mass (1, 1942)
- Karshan, Maxwell, Ph D Department of Biological Chemistry, Columbia University, 630 W 168th St, New York City Associate Professor of Biochemistry (2, 1939)
- Karsner, Howard T, M D Western Reserve University, 2085 Adelbert Rd, Cleveland, O Professor of Pathology, Director of the Institute of Pathology (4, 1913, 6, 1925)
- Katz, Gerhard, M D Lynchburg State Colony, Colony, Virginia Clinical Director (3, 1937)
- Katz, Louis Nelson, A M, M D 2900 Ellis Ave, Chicago, Ill Director of Cardiovascular Research, Michael Reese Hospital, Professorial Lecturer in Physiology, University of Chicago (1, 1924)
- Katzman, Philip A, Ph D St Louis University School of Medicine, 1402 S Grand Blvd, St Louis 4, Mo Associate Professor of Biochemistry (2, 1935)
- Kaulbersz, Jerzy, Ph D, M D Wayne University College of Medicine, 1512 St Antoine St, Detroit, Mich Research Associate in Surgery and Research Physiology (1, 1911)
- Kay, H D, Ph D, D Sc, I R S National Institute for Research in Dairying, Shinfield, near Reading, England Director, Research Professor of Biochemistry, University of Reading (2, 1930)
- Keeton, Robert W, M S, M D University of Illinois College of Medicine, 1853 W Polk St, Chicago Professor of Medicine (1, 1916, 3, 1921)
- Kehoe, Robert A, M D Kettering Laboratory of Applied Physiology, College of Medicine, University of Cincinnati, Eden Ave, Cincinnati, O Research Professor of Physiology (1, 1940)
- Keith, Norman M, M D Mayo Clinic, Rochester, Minn Consulting Physician, Division of Medicine, Mayo Clinic, Professor of Medicine, Mayo Foundation, University of Minnesota (1, 1920, 3, 1932, 4, 1921)
- Keith, T B, Ph D Animal Industry and Range Management, Agricultural Experiment Station, Bozeman, Mont Associate Professor (5, 1941)
- Keller, Allen D, Ph D Baylor College of Medicine, Houston, Texas Professor of Physiology, Chairman of Department of Physiology and Pharmacology (1, 1931)
- Kelser, Raymond A, D V M, Ph D 130 Valley Rd, Ardmore, Pa Professor of Bacteriology and Dean of Faculty School of Veterinary Medicine, University of Pennsylvania, Philadelphia, Pa (4, 1932)
- Kelsey, F Ellis, B S, Ph D University of Chicago, Chicago, Ill Research Associate (Instructor) in Pharmacology (3, 1941)
- Kelsey, Frances Kathleen O, M S, Ph D University of Chicago, Chicago, Ill Research Assistant in Pharmacology (3, 1941)
- Kemmerer, A R, Ph D University of Arizona, Tucson, Arizona Head, Dept of Human Nutrition (5, 1946)
- Kempner, Walter, M D Duke University School of Medicine, Durham, N C Assistant Professor of Medicine (1, 1940)
- Kendall, Edward C, M S, Ph D, D Sc 627 Eighth Ave, S W, Rochester, Minn Professor of Biochemistry, Mayo Foundation, University of Minnesota (1, 1916, 2, 1913, 4, prior to 1920)
- Kendall, Forrest E, Ph D 240-06-53rd Ave Douglaston, Long Island, N Y Assistant Professor of Biochemistry, Research Service, Columbia Division, Goldwater Memorial Hospital, Welfare Island, N Y (6, 1943)
- Kennard, Margaret A, M D Psychiatric Division,

- Bellevue Hospital, First Ave & 30th St, New York City (1, 1934)
- Kennedy, Cornelia, M A, Ph D Snyder Hall, University Farm, St Paul, Minn Associate Professor of Agricultural Biochemistry, University of Minnesota, Assistant Chemist, Minnesota Experiment Station (2, 1921, 5, 1934)
- Kennedy, Robert P, M D Knollwood Drive, R D 1, Rochester, N Y (4, 1929)
- Kenton, Harold B, Ph D New England Deaconess Hospital, Boston, Mass Bacteriologist and Director of the Blood Bank (6, 1931)
- Kenyon, Allan T, M D University of Chicago, Division of Biological Sciences, 950 E 59th St, Chicago, Ill Assistant Professor of Medicine (3, 1940)
- Keresztes, John C, M A, Ph D Cancer Research, Mt Sinai Hospital, Fifth Ave and 100th St, New York 19, N Y (2, 1941, 5, 1945)
- Kerr, Stanley E Ph D American University of Beirut, Beirut, Lebanon, Syria Professor of Biological Chemistry (2, 1937)
- Kerr, Wm J, M D University of California Hospital, Third and Parnassus Aves, San Francisco Professor of Medicine, University of California, Physician-in Chief, University of California Hospital (3, 1930)
- Kesten, Homer D, M D College of Physicians and Surgeons, Columbia University, New York City Associate Professor of Pathology (4, 1931)
- Kety, Seymour S, M D Dept of Pharmacology, Medical School, University of Pennsylvania, Philadelphia 4 Associate in Pharmacology, Medical School, Assistant Visiting Physician in Medicine, Philadelphia General Hospital (3, 1945)
- Keys, Ancel, M A, Ph D, D Phil Stadium South Tower, University of Minnesota, Minneapolis Professor and Director of Laboratory of Physiological Hygiene (1, 1939, 2, 1936)
- Khorazo, Deborah, M D Apt 4G, 480 W 187th St, New York City Instructor in Bacteriology, Columbia University, Eye Institute (6, 1936)
- Kidd, John G, M D Cornell University Medical College, 1300 York Ave, New York City Professor of Pathology, Pathologist, New York Hospital (4, 1938, 6, 1937)
- Kik, M C, Ph D College of Agriculture, University of Arkansas, Fayetteville Associate Professor of Agricultural Chemistry (5, 1942)
- Kilborn, Leslie G, M A, M D, Ph D 47 Warren Road, Toronto, Ontario, Canada (1, 1928)
- Killian, John Allen, A M, Ph D Killian Research Laboratories, Inc, 49 W 45th St, New York City (2, 1921)
- King, Barry G, M A, Ph D College of Physicians and Surgeons, Columbia University, 630 West 168th St, New York City Assistant Professor of Physiology, Lieutenant, USNR, Naval Medical Research Institute, Bethesda, Md (1, 1938)
- King, Charles Edwin, Ph D Vanderbilt University, Nashville, Tenn Associate Professor of Physiology (1, 1916)
- King, Charles Glen, Ph D Nutrition Foundation, Inc, Chrysler Building, New York City Scientific Director, Professor of Chemistry, Columbia University (2, 1931, 5, 1933)
- King, Jessie Luella, Ph D Goucher College, Baltimore, Md Professor of Physiology (1, 1914)
- King, Joseph T, M D, Ph D 314 Millard Hall, University of Minnesota Medical School, Minneapolis Associate Professor of Physiology (1, 1931)
- King, Lester S, M D Illinois Masonic Hospital, Chicago, Ill Director of Laboratories, Clinical Assistant Professor of Pathology, University of Illinois (4, 1941)
- Kirk, Paul L, Ph D University of California, Berkeley Professor of Biochemistry (2, 1933)
- Kirkbride Mary B, Sc D 314 State St, Albany 6, N Y (6, 1921)
- Kisch, Bruno, M D 845 West End Ave, New York City Professor of Biochemistry, Yeshiva University (1, 1943)
- Kleiber, M, D Sc University of California, Davis Professor of Animal Husbandry (1, 1943, 5, 1933)
- Klein, J Raymond, Ph D University of Illinois, Neuropsychiatric Institute, 912 S Wood St, Chicago Biochemist and Assistant Professor of Psychiatry and Physiological Chemistry (2, 1941)
- Kleiner, Israel Simon, Ph D New York Medical College, Flower and Fifth Avenue Hospitals, New York 29, N Y Professor of Physiology and Biochemistry (1, 1911, 2, 1912, 3, 1912, 5, 1933)
- Kleitman, Nathaniel, A M, Ph D University of Chicago, Chicago, Ill Associate Professor of Physiology (1, 1923)
- Klemperer, Friedrich Wilhelm, M D, Massachusetts General Hospital, Boston, Mass Assistant in Medicine (2, 1941)
- Kletzien, Seymour W, M S, Ph D, 22 Lafayette Blvd, Williamsville, N Y Biochemist (5, 1933)
- Kline, O L, Ph D Federal Security Agency, Food and Drug Administration, Washington, D C Biochemist (5, 1936)
- Kline, Raymond F, B S, M S Physiological Lab Univ of Virginia Med School, Charlottesville, Va Instructor in Physiology (1, 1946)

- Kluver, Heinrich**, Ph D University of Chicago, Chicago, Ill *Professor of Experimental Psychology* (1, 1935)
- Knight, C Arthur, Jr**, Ph D The Rockefeller Inst for Med Research, Princeton, N J *Associate* (2, 1946)
- Knoefel, Peter K**, M A, M D University of Louisville, 101 W Chestnut St, Louisville, Ky *Professor of Pharmacology* (3, 1934)
- Knowlton, Frank P**, A M, M D Syracuse University College of Medicine, Syracuse, N Y *Emeritus Professor of Physiology* (1, 1911)
- Knowlton, G Clinton**, Ph D 419 S Summit St, Iowa City, Iowa (1, 1938)
- Knudson, Arthur**, Ph D Albany Medical College, New Scotland Ave, Albany, N Y *Professor of Biochemistry and Associate Dean* (2, 1919, 5, 1936)
- Knutti, Ralph Eddy**, M D Children's Hospital, Los Angeles, Calif *Director of Laboratories, Assistant Professor of Pathology, University of Southern California* (4, 1933)
- Kober, Philip A**, B S Sherman Laboratories, Detroit, Mich *Director of Research* (2, 1912)
- Koch, Elizabeth M**, M A, Ph D 1534 E 59th St, Chicago, Ill (2, 1925)
- Koch, Fred Conrad**, M S, Ph D 1534 East 59th St, Chicago, Ill *Director of Biochemical Research, Armour Laboratories, Professor of Biochemistry Emeritus, University of Chicago* (2, 1912, 5, 1933)
- Kochakian, Charles D**, A M, Ph D University of Rochester Medical School, 260 Crittenden Blvd, Rochester, N Y *Assistant Professor, Dept of Vital Economics* (1, 1942)
- Kocher, Rudolph Alfred**, M D Box 926, Carmel, Calif *Director, Velde Metabolic Clinic* (2, 1915)
- Koehler, Alfred E**, M D, Ph D 317 W Pueblo St, Santa Barbara, Calif *Physician, Sansum Clinic, Santa Barbara Cottage Hospital* (2, 1924)
- Koehne, Martha**, Ph D 285 15th Ave, Apt 22, Columbus, Ohio *Nutritionist, Ohio State Dept of Health* (5, 1933)
- Koepf, George F**, M D 109 Linwood Ave, Buffalo 9, N Y *Instructor of Medicine and Associate in Physiology, University of Buffalo* (1, 1942)
- Koerber, Walter L**, Ph D E R Squibb & Sons, New Brunswick, N J *Assistant Department Head* (6, 1943)
- Kohn, Henry I**, Ph D Bellevue Hospital, 27th St and 1st Ave, New York 16, N Y (1, 1940)
- Kolmer, John A**, M S, M D, D P H, Sc D, LL D, L H D 1 Montgomery Ave, Bala-Cynwyd, Pa *Professor of Medicine, Temple University, Director, Research Institute of Cutaneous Medicine* (6, 1913)
- Komarov, Simon A**, M S, M D, Ph D S S Fels Fund, Med Research Laboratory, 255 S 17th St, Philadelphia, Pa *Director of Dept of Biochemistry* (1, 1933)
- Kopeloff, Nicholas**, Ph D New York State Psychiatric Institute, 722 W 168th St, New York City *Principal Research Bacteriologist, New York State Psychiatric Institute and Hospital* (6, 1937)
- Koppanyi, Theodore**, Ph D Georgetown University, Washington, D C *Professor of Pharmacology* (1, 1921, 3, 1935)
- Korr, Irwin M**, M A, Ph D Still Memorial Research Trust, Kirksville, Mo (1, 1939)
- Kozelka, Frank L**, Ph D Dept of Pharmacology and Toxicology, University of Wisconsin, Madison *Assistant Professor of Toxicology On leave Captain, Sn C* (3, 1939)
- Krahl, Maurice E**, Ph D Washington Univ School of Medicine, St Louis 10, Mo *Assistant Professor of Pharmacology* (2, 1939)
- Krakower, Cecil Alexander**, M D University of Illinois College of Medicine, 1853 West Polk St, Chicago *Associate Professor of Pathology* (4, 1945)
- Kramer, Benjamin**, A M, M D 60 Plaza St, Brooklyn, N Y *Pediatrician-in-Chief, Brooklyn Jewish Hospital, Professor of Clinical Pediatrics, Long Island College Medical School* (1, 1915, 2, 1914)
- Kramer, Martha**, Ph D Department of Home Economics, Yenching University, Peiping, China *Professor of Food Economics and Nutrition* (5, 1933)
- Kramer, S D**, M D, Ph D 92 Washington Square, East Salem, Mass *Virologist* (6, 1944)
- Krampitz, Lester O**, Ph D Dept of Bacteriology, Iowa State College, Ames, Iowa *Assistant Professor* (2, 1946)
- Krantz, John C, Jr**, M S, Ph D University of Maryland Medical School, Baltimore *Professor of Pharmacology* (3, 1937)
- Krauss, William E**, Ph D Ohio Experiment station, Wooster Chief, *Department of Dairy Industry, Ohio State University, Chairman, Department of Dairy Husbandry* (2, 1932, 5, 1933)
- Kraybill, Henry R**, M S, Ph D 5720 Woodlawn Ave, Chicago 37, Ill *Professorial Lecturer, Department of Biochemistry, University of Chicago, Director, Department of Scientific Research, American Meat Institute* (2, 1942)
- Krayer, Otto**, M D Harvard Medical School, 25 Shattuck St, Boston, Mass *Associate Professor of Comparative Pharmacology* (3, 1938)

- Krop, Stephen, Ph D War Department, Chemical Warfare Service, Edgewood Arsenal, Edgewood, Maryland (3, 1941)
- Krueger, Albert Paul, M D Captain M C, USNR 3517 Life Sciences Bldg, University of California, Berkeley *Professor of Bacteriology, Commanding Officer U S N Medical Research Unit No 1, Berkeley, Calif* (1, 1930, 6, 1937)
- Krueger, Hugo M, Ph D American Univ of Beirut, Beirut, Lebanon, Syria *Director of Dept of Pharmacology* (1, 1931, 3, 1935)
- Krumbhaar, Edward B, M D, Ph D University of Pennsylvania Medical School, Philadelphia *Professor of Pathology* (1, 1911, 1, prior to 1920)
- Kruse, Harry Dayton, M D, Sc D Milbank-Memorial Fund, 40 Wall St, New York City (2, 1933)
- Kruse, Theophile K, A M, Ph D University of Pittsburgh Medical School, Pittsburgh, Pa *Professor of Physiology and Pharmacology* (1, 1919, 3, 1920)
- Kubie, Lawrence S, M D 7 E 81st St, New York City *Associate in Neurology, College of Physicians and Surgeons, Columbia University* (4, 1928)
- Kuhn, Harry A, M S, Ph B 3915 Fulton St, N W, Washington, D C Colonel C W S, War Department, Executive Officer, C W Procurement District (3, 1927)
- Kuhn, L Roland, Ph D 6th Army Area Lab Presidio, Monterey, Calif *Major, U S Bacteriologist* (6 1939)
- Kunde, Margarete M, Ph D, M D 30 N Michigan Ave, Chicago, Ill *Instructor in Medicine, Northwestern University Medical School, Clinical Assistant in Endocrinology, Cook County Hospital* (1, 1924)
- Kurtz, Alton C, Ph D Department of Biochemistry, Medical School, University of Oklahoma, Oklahoma City *Associate Professor* (2, 1942)
- Kuyper, Adrian C, M S, Ph D Wayne University College of Medicine, Detroit 26, Mich *Assistant Professor of Physiological Chemistry* (2, 1946)
- Kydd, David M, M D Mary Imogene Bassett Hospital, Cooperstown, N Y *Associate Physician* (5, 1934)
- Kyes, Preston, A M, Sc D, M D North Jay, Me *Professor Emeritus of Preventive Medicine, University of Chicago* (6, 1918)
- Lacy, G R, M D University of Pittsburgh, Pittsburgh, Pa *Professor of Bacteriology and Immunology* (4, 1927)
- Lalich, Joseph J, M D Dept of Pathology, University of Wisconsin, 426 North Charter St, Madison 6, Wis *Instructor in Pathology* (4, 1946)
- Lamb, Alvin R, M S, Ph D Experiment Station, Hawaiian Sugar Planters' Association, Honolulu *Research Associate* (2, 1923, 5, 1931)
- Lambert, Edward H, Ph D, M D Mayo Aero Medical Unit, Mayo Foundation, Rochester, Minn *Associate in Physiology* (1, 1945)
- Lambert, Robert A, M D Rockefeller Foundation, 49 W 49th St, New York City *Associate Director for the Medical Sciences* (4, 1922)
- Lamport, Harold, M D Yale University School of Medicine, New Haven, Conn *Associate Professor of Physiology* (1, 1943)
- Lamson, Paul Dudley, M D Vanderbilt University Medical School, Nashville, Tenn *Professor of Pharmacology* (1, 1921, 3, 1915)
- Lamson, Robert W, A M, Ph D, M D Suite S10, 1930 Wilshire Blvd, Los Angeles, Calif *Professor of Medicine and Public Health, University of Southern California School of Medicine* (6, 1928)
- Lancefield, Rebecca C, Ph D 4 Kenmore Rd, Douglaston, Long Island, N Y *Associate Member, Rockefeller Institute for Medical Research* (6, 1933)
- Landis, Carney, Ph D Psychiatric Institute and Hospital, Columbia University, 722 W 168th St, New York City *Principal Research Psychologist and Professor of Psychology* (1, 1939)
- Landis, Eugene Markley, Ph D, M D Department of Physiology, Harvard Medical School, 25 Shattuck St, Boston, Mass *George Higginson Professor of Physiology* (1, 1928)
- Lands, Alonzo M, M A, Ph D Frederick Stearns and Co, 6533 Jefferson Ave, Detroit, Mich *Director, Pharmacologic Research* (1, 1942)
- Lange, Carl, M D 371 Morris St, Albany, N Y *Associate Bacteriologist, Divisions of Laboratories and Public Health, New York State Department of Health* (6, 1938)
- Langley, Wilson D, Ph D University of Buffalo Medical School, Buffalo, N Y *Associate Professor of Biological Chemistry* (2 1937)
- Langworthy, Orthello R, M A, M D Johns Hopkins Hospital, Baltimore, Md *Associate Professor of Neurology, Johns Hopkins University* (1, 1928)
- Lardy, Henry A, M S, Ph D Dept of Biochemistry, University of Wisconsin, Madison 6, Wis *Assistant Professor* (2, 1946)
- Larrabee, Martin G, Ph D Johnson Foundation, for Medical Physics, University of Pennsylvania, Philadelphia *Assistant Professor of Biophysics* (1, 1940)

- Larson, Edward**, Ph D Temple University Medical School, Broad and Ontario Sts, Philadelphia, Pa *Associate Professor of Pharmacology* (1, 1929, 3, 1937)
- Larson, Hardy W**, A M, Ph D Metropolitan Life Insurance Co, Biochemical Laboratory, 1 Madison Ave, New York City *Research Chemist* (2, 1937)
- Larson, Paul S**, Ph D Medical College of Virginia, Richmond *Associate in Physiology and Pharmacology* (1, 1939)
- Larson, W P**, M D University of Minnesota, Minneapolis *Professor and Head of Department of Bacteriology and Immunology* (6, 1917)
- Lashley, K S**, M S, Ph D, D Sc Yerkes Laboratories, Orange Park, Fla *Research Professor of Neuropsychology, Harvard University, Director, Yerkes Laboratories of Primate Biology, Inc Member of the National Academy of Sciences* (1, 1923)
- Laskowski, M**, Ph D Marquette University Medical School, Milwaukee 3, Wis *Associate Professor of Biochemistry* (2, 1911)
- Lauffer, Max A, Jr**, M S, Ph D 307 Flaw Hall, University of Pittsburgh, Pittsburgh, Pa *Associate Research Professor* (2, 1916)
- Laug, E P**, M A, Ph D Division of Pharmacology, Food and Drug Administration, Federal Security Agency, Washington 25, D C *Senior Pharmacologist* (2, 1938)
- Laurens, Henry**, A M, Ph D, LL D P O Box 157, Flat Rock, N C *Professor of Physiology* (1, 1913)
- Lauson, Henry D**, Ph D, M D The Rockefeller Institute, 66th St & York Ave, New York 21, N Y *Associate* (1, 1916)
- Lavine, T F**, Ph D Lankenau Hospital Research Institute, Philadelphia, Pa *Research Chemist* (2, 1938)
- Lawrence, W Sherwood**, M D Dept of Pharmacology, University of Michigan, Ann Arbor *Instructor of Pharmacology* (3, 1944)
- Lawson, Hampden**, M D, Ph D University of Louisville, Louisville, Ky *Professor of Physiology* (1, 1933)
- Leake, Chauncey D**, M S, Ph D The University of Texas Medical Branch, Galveston *Vice-President of the University of Texas in Charge of the Medical Program* (1, 1923, 3, 1924)
- Leathem, James H**, Ph D Rutgers University, New Brunswick, N J *Assistant Professor of Zoology* (1, 1945)
- Leathes, John Beresford**, M A, M B, F R C S, F R S 106 Banbury Rd, Oxford, England (2, 1909)
- Lederer, Ludwig George**, Ph D, M D Pennsylvania Central Airlines, National Airport, Washington, D C *Medical Director* (1, 1940)
- Lee, Milton O**, M A, Ph D Harvard Medical School, Boston, Mass *Associate, Memorial Foundation for Neuroendocrine Research, Director of Laboratory, Worcester State Hospital* (1, 1927, 5, 1933)
- Lee, Robert Cleveland**, B Ch E, M A 309 Bellevue St, Newton, Mass *Member of Research Staff, Nutrition Lab, Carnegie Institution of Washington* (1, 1911, 5, 1919)
- Leese, Chester E**, M S, Ph D George Washington University School of Medicine, Washington, D C *Associate Professor of Physiology* (1, 1931)
- Lehman, Arnold J**, Ph D, M D Food and Drug Administration, Washington 25, D C *Chief, Division of Pharmacology* (3, 1937)
- Lehman, Robert A**, M S, Ph D New York University College of Medicine, 477 First Ave, New York City *Instructor in Therapeutics* (3, 1942)
- Lehmann, Gerhard**, M D, Dr Ing Hoffmann La Roche, Scientific Dept, Nutley 10, N J *Pharmacologist* (3, 1939)
- Lehninger, Albert L**, M S, Ph D University of Chicago Medical School, Chicago, Ill *Assistant Professor of Biochemistry in the Depts of Biochemistry and Surgery* (2, 1916)
- Lein, Allen**, B A, M A, Ph D Department of Physiology, Vanderbilt University School of Medicine, Nashville, Tenn *Physiologist* (1, 1916)
- Lenhart, Carl H**, M D Lakeside Hospital, 2065 Adelbert Rd, Cleveland, O *Oliver H Payne Professor of Surgery, Western Reserve University* (1, 1921)
- Lenette, Edwin H**, Ph D, M D Chief, Biological Research Division, Camp Detrick, Frederick, Md (4, 1911)
- Leonard, Clifford Shattuck**, M S, Ph D University of Vermont Medical College, Burlington *Assistant Professor of Pharmacology* (3, 1927)
- Lepkovsky, Samuel**, M S, Ph D University of California, Berkeley *Associate Professor of Poultry Husbandry* (2, 1933, 5, 1933)
- L'Esperance, Elise L**, M D 2 East 61st St, New York, N Y *Director, Strong Cancer Precaution Clinic, Memorial Hospital, and New York Infirmary* (6, 1920)
- Leverton, Ruth M**, Ph D Department of Home Economics, University of Nebraska, Lincoln *Associate Professor Human Nutrition Research* (5, 1942)
- Levin, Louis**, Ph D College of Physicians and Surgeons, Columbia Univ, 630 W 168th St, New York 32, N Y *Assistant Professor of Anatomy* (2, 1939)
- Levine, Harold**, Ph D Pabst Brewing Co, 917 W Juneau Ave, Milwaukee, Wis *Biochemist* (2, 1933, 5, 1933)

- Levine, Milton, M S, Ph D Inst of Experimental Medicine, College of Medical Evangelists, 312 N Boyle Ave, Los Angeles, Calif (6, 1912)
- Levine, Philip, M A, M D, L A C P Ortho Research Foundation, Raritan, N J Director, *Biologic Division* (6, 1925)
- Levine, Rachmuel, M D, C M Michael Reese Hospital, Chicago, Ill Acting Director, *Department of Metabolic Research* (1, 1912)
- Lerine, Samuel Z, M D, New York Hospital, 525 E 68th St, New York City Professor of Pediatrics, Cornell University Medical College, Pediatrician-in-Chief, New York Hospital (5, 1933)
- Levine, Victor Emanuel, A M, M D, Ph D Ninth Service Command Laboratory, Presidio of Monterey, California Lt Colonel (2, 1936)
- Levinson, Samuel A Ph D, M D University of Illinois College of Medicine, 808 S Wood St, Chicago Professor of Pathology, Director Laboratories, Research & Educational Hospital (1, 1933)
- Levison, Louis A, M D 421 Michigan St, Toledo, O Physician to Toledo Hospital, Physician to St Vincent Hospital (6, 1916)
- Lery, Milton, Ph D 477 First Ave, New York City Assistant Professor of Chemistry, New York University College of Medicine (2, 1933)
- Lery, Robert L, M D 730 Park Ave, New York City Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University (3, 1915)
- Lewey, F H, M D University Hospital, University of Pennsylvania, Philadelphia Visiting Professor of Neurophysiology and Consultant in Neurology Major (MC), IUS (1, 1937)
- Lewis, Gladys Kinsman, M A, Ph D 401 S Lafayette St, Denver 9, Colo (5, 1944)
- Lewis, Howard Bishop, Ph D Medical School, University of Michigan, Ann Arbor Professor of Biological Chemistry and Director of the College of Pharmacy (1, 1925, 2, 1913, 5, 1933)
- Lewis, James C, M S, Ph D Western Regional Research Laboratory, U S Dept of Agriculture, Albany 6, Calif Associate Biochemist (2, 1946)
- Lewis, Julian Herman, M D 4750 Champlain Ave, Chicago, Ill Associate Professor of Pathology, University of Chicago, Member of the Otto S A Sprague Memorial Institute (4, 1924)
- Lewis, Lena A, A B, M A, Ph D Cleveland Clinic, Euclid Ave & E 93rd St, Cleveland 6, Ohio Research Staff (1, 1946)
- Lewis, Robert C, Ph D 4200 E 9th Ave, Denver, Colo Professor of Biochemistry, School of Medicine, University of Colorado (2, 1931, 5, 1933)
- Lewis, Warren H, M D The Wistar Institute of Anatomy and Biology, Woodland Ave and 36th St, Philadelphia, Pa Member, Member of the National Academy of Sciences (1, 1919)
- Li, Choh Hao, Ph D 1596 Life Science Bldg, University of California, Berkeley Assistant Professor of Experimental Biology and Lecturer in Anatomy (2, 1911)
- Li, Richard D, M D Peiping Union Medical College, Peiping, China Instructor in Pharmacology (3, 1911)
- Libby, Raymond L, M S, Ph D American Cyanamid Co, 1937 W Main St, Stamford, Conn Bio-physicist (6, 1938)
- Libet, Benjamin, Ph D Univ of Chicago, Chicago 37, Ill Instructor in Physiology (1, 1912)
- Lubman, Emanuel, M D 180 E 64th St, New York City Consulting Physician, Mount Sinai Hospital (6, 1920)
- Liddell, Howard S, A M, Ph D Cornell University, Ithaca, N Y Professor of Psychology (1, 1925)
- Lieb, Charles C, M D 630 W 168th St, New York City Hosac Professor of Pharmacology, College of Physicians and Surgeons Columbia University (1, 1936, 3, 1915)
- Lieberman, Arnold L, M D, Ph D 323 No Country Club Road, Tucson, Ariz (1 1934)
- Lifson, Nathan, M D, Ph D 617 Kenwood Parkway, Minneapolis, Minn Associate Professor of Physiology, University of Minnesota Medical School (1, 1911)
- Lightbody, Howard D, M S, Ph D Western Regional Research Laboratory, U S Department of Agriculture, Albany 6, Calif Principal Biochemist (2, 1936)
- Lilienthal, Joseph L, M D Johns Hopkins Hospital, Baltimore 5, Md (1, 1945)
- Lillie, Ralph Stayner, Ph D, Sc D University of Chicago, Chicago, Ill Professor Emeritus of General Physiology, Physiologist, Marine Biological Laboratory, Woods Hole, Mass (1, 1905, 2, 1913)
- Lillie, R D, M D Chief Pathology Laboratory, National Institute of Health, Bethesda, Md Medical Director, U S P H S (4, 1941)
- Lim, Robert Kho-Seng, Ph D, D Sc, F R S E Peiping Union Medical College, Peiping, China Professor of Physiology (1, 1923)
- Lindsley, Donald B, M A, Ph D Dept of Psychology, Northwestern Univ, Evanston, Ill (1, 1937)
- Linegar, Charles R, Ph D E R Squibb and Sons, Biological Laboratory, New Brunswick, N J Chief, Biological Development and Control Laboratory (3, 1938)
- Lineweaver, Hans, M A, Ph D Western Regional Research Laboratory, U S Department of Agriculture, Albany 6, Calif Senior Biochemist (2, 1941)

- Link, Karl Paul, Ph D Biochemistry Building, University of Wisconsin, Madison *Professor of Biochemistry* (2, 1931)
- Lintz, William, M D 36 Plaza St, Brooklyn, N Y *Late Professor of Immunology and Bacteriology and Clinical Professor of Medicine, Long Island College of Medicine* (6, 1920)
- Lipman, Mrs Miriam O, A M Presbyterian Hospital, 620 W 168th St, New York City *Research Assistant, Edward Daniels Faulner Arthritis Clinic* (6, 1931)
- Lipmann, Fritz, M D, Ph D Biochemical Research Laboratory, Massachusetts General Hospital, Boston *Research Chemist, Head, Biochemical Research Laboratory, Research Fellow in Biochemistry and Surgery, Harvard Medical School* (2, 1941)
- Lipton, Morris A, Ph D 5615 S Maryland Ave, Chicago 37, Ill *Research Associate in Medicine, University of Chicago* (2, 1916)
- Litchfield, John T, Jr, M D American Cyanamid Co, 1937 W Main St, Stamford, Conn *Director of Pharmacology* (3, 1910)
- Little, James Maxwell, M S, Ph D Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N C *Assistant Professor of Physiology and Pharmacology* (1, 1912)
- Livingston, Alfred E, Ph D Temple University School of Medicine, Philadelphia, Pa *Professor of Pharmacology* (1, 1917, 3, 1920)
- Lloyd, David P C, D Ph Rockefeller Inst for Medical Research, 66th St and York Ave, New York 21, N Y *Associate Member* (1, 1939)
- Locke, Arthur P, Ph D Zonite Products Corporation, New Brunswick, N J *Chief Research Chemist* (6, 1926)
- Lodholz, Edward, M D Medical Laboratories, University of Pennsylvania, Philadelphia *Isaac Ott Professor of Physiology, Graduate School of Medicine* (1, 1913)
- Loeb, Leo, M D Washington University Medical School, St Louis, Mo *Professor Emeritus of Pathology, Member, National Academy of Sciences* (1, 1907, 4, 1913)
- Loebel, Robert O, M D Russell Sage Institute of Pathology, Cornell Medical College, 1300 York Ave, New York City *Research Fellow, Adjunct Assistant Visiting Physician, Second (Cornell) Medical Division of Bellevue Hospital* (1, 1928)
- Loew, Earl R, M S, Ph D Univ of Ill College of Med, 1853 W Polk St, Chicago 12 *Associate Professor of Pharmacology* (1, 1940, 3, 1946)
- Loewe, W S, M D 17 Cole Terrace, New Rochelle, N Y *Hon Prof Pharmacology, Heidelberg, Dept of Pharmacology, Cornell University Medical College* (3, 1936)
- Logan, Milan A, Ph D University of Cincinnati School of Medicine, Cincinnati, O *Professor of Biological Chemistry* (2, 1936)
- Long, C N II, M Sc, D Sc, M D Yale University, New Haven, Conn *Sterling Professor of Physiological Chemistry* (1, 1935, 2, 1927)
- Long, Esmond R, M D 7th and Lombard Sts, Philadelphia, Pa *Director, Henry Phipps Institute, Professor of Pathology, University of Pennsylvania* (4, 1930)
- Long, Perrin Hamilton, M D The Johns Hopkins University, 615 N Wolfe St, Baltimore, Md *Professor of Preventive Medicine, Colonel, M C* (3, 1910)
- Longcope, Warfield T, M D Cornhill Farm, Lee, Miss (3, 1921, 4, 1913, 6, 1923)
- Longenecker, Herbert Eugene, M S, Ph D University of Pittsburgh Pittsburgh, Pa *Dean the Graduate School and Professor of Biochemistry* (2, 1910, 5, 1915)
- Longwell, Bernard B, M S, Ph D 1200 East 9th Ave, Denver 7, Colo *Associate Professor of Biochemistry, Univ of Colorado, School of Medicine* (2, 1916)
- Looney, Joseph M, M D 190th General Hospital, APO #562, c/o Postmaster, New York City *Lt Colonel, U S A* (2, 1922)
- Loosli, Clayton Gurr, M D, University of Chicago, Chicago, Ill *Associate Professor of Medicine* (1, 1910)
- Loosli, J K, M S, Ph D Animal Nutrition Laboratory, Cornell University, Ithaca, N Y *Assoc Prof of Animal Nutr and Assoc Animal Nutritionist in Exp Sta* (5, 1911)
- Lorber, Victor, M D, Ph D Dept of Biochemistry, Western Reserve Univ School of Medicine, Cleveland, Ohio *Associate Professor* (1, 1944)
- Lorente de Nó, Rafael, M D The Rockefeller Institute for Medical Research, 66th St and York Ave, New York City *Member* (1, 1937)
- Lorenz, Egon, Ph D National Cancer Institute, Bethesda, Md *Senior Biophysicist* (4, 1942)
- Loring, H S, M S, Ph D Stanford University, Calif *Associate Professor of Biochemistry* (2, 1938)
- Loveless, Mary H, M D New York Hospital, 525 E 68th St, New York City *Research Associate, Cornell Medical School, Physician to Out-Patients, New York Hospital* (6, 1941)
- Lowell, Francis C, M D Nine Acre Corner, Concord, Mass *Instructor in Medicine, Boston City Hospital* (6, 1942)
- Lowenbach, Hans, M D Duke University Medical School, Durham, N C *Asst Professor of Neuropsychiatry and Physiology* (1, 1946)
- Lowry, Oliver H, M D, Ph D Research Laboratory, Public Health Research Institute of the City of New York, Foot of E 15th St *Research Associate* (2, 1942)

- Lubinski, Herbert, M D Jewish General Hospital, 3755 St Catherine Rd, Montreal, Canada *Bacteriologist* (6, 1911)
- Lucas, Colin C, M A Sc, Ph D Banting and Best Dept of Medical Research, University of Toronto, Toronto, Canada *Associate Professor* (2, 1946)
- Lucas, George H W, M A, Ph D University of Toronto, Toronto, Canada *Associate Professor of Pharmacology* (2, 1925, 3, 1928)
- Luck, James Murray, Ph D Stanford University, Stanford, Calif *Professor of Biochemistry* (2, 1925)
- Lucké, Balduin, M D 141 Montgomery Ave, Bal Cynwyd, Pa *Professor of Pathology, University of Pennsylvania Medical School* (4, 1924)
- Luckhardt, Arno Benedict, M S, Ph D, M D, Sc D, LL D University of Chicago, Chicago, Ill *Professor of Physiology* (1, 1911)
- Ludewig, Stephan, Ph D University of Virginia School of Medicine, University *Associate Professor of Biochemistry* (2, 1941)
- Luduena, Froilan P, Ph D, M D Department of Pharmacology, Stanford University Medical School, San Francisco, Calif *Assistant Professor of Pharmacology* (3, 1941)
- Lukens, Francis D W, M D University of Pennsylvania, 809 Maloney Clinic, 36th and Spruce Sts, Philadelphia *Assistant Professor of Medicine and Director, George S Cox Medical Research Institute* (1, 1938)
- Lund, E J, Ph D Department of Zoology and Physiology, University of Texas, Austin *Professor of General Physiology* (1, 1930)
- Lundgren, Harold P, Ph D Western Regional Research Laboratory, U S D A, Albany 6, Calif *Senior Chemist* (2, 1942)
- Lundy, John Silas, M D The Mayo Foundation, Rochester, Minn *Chief of Section on Anesthesia* (3, 1935)
- Lurie, Max B, M D Henry Phipps Institute, 7th and Lombard Sts, Philadelphia, Pa *Associate Professor of Experimental Pathology* (4, 1934, 6, 1930)
- Lutz, Brenton R, Ph D Boston University, 688 Boylston St, Boston, Mass *Professor of Biology* (1, 1925)
- Luyet, Basile J, Sc D (Biol), Sc D (Physics) St Louis University School of Medicine, St Louis, Mo *Professor of Biology* (1, 1936)
- Lyall, Harold W, A M, Ph D Division of Laboratories and Research, New York State Department of Health, Albany *Assistant Director in charge of Antitoxin, Serum, and Vaccine Laboratories* (6, 1937)
- Lyman, Carl M, Ph D Division of Swine Husbandry, Agricultural Experiment Station, College Station, Texas *Nutritionist* (2, 1940)
- Lyman, John F, Ph D Townshend Hall, Ohio State University, Columbus *Professor of Agricultural Chemistry* (2, 1920, 5, 1933)
- Maaske, Clarence A, Ph D University of Colorado School of Medicine, 4200 E 9th Ave, Denver, Colo *Associate Professor of Physiology and Pharmacology* (1, 1915)
- Macallum, A Bruce, M D, Ph D Medical School, University of Western Ontario, London, Ont, Canada *Professor of Biochemistry* (2, 1914)
- MacArthur, Edith H, A M, Ph D Skidmore College, Saratoga Springs, N Y *Professor and Director of Home Economics* (5, 1933)
- MacCorquodale, D W, M S, Ph D Abbott Laboratories, North Chicago, Ill *Head, Biochemical Research* (2, 1934)
- MacFadyen, Douglas A, M A, M D Rush-Presbyterian Hospital Division, University of Illinois College of Medicine, 1753 West Congress St, Chicago 12, Ill *Professor of Biochemistry* (2, 1912)
- MacKay, Eaton M, M D The Scripps Metabolic Clinic, La Jolla, Calif (1, 1930)
- Mackenzie, Cosmo G, A B, Sc D Dept of Biochemistry, Cornell Univ Med College, 1300 York Ave, New York 21, N Y *Research Associate* (1, 1946, 2, 1946, 5, 1942)
- Mackenzie, George M, M D Mary Imogene Bassett Hospital, Cooperstown, N Y *Physician-in-Chief, Director, Otsego County Laboratories* (6, 1921)
- MacLeod, Colin M, M D New York University College of Medicine, 477 First Ave, New York City *Professor of Bacteriology* (6, 1937)
- MacLeod, Florence L, M A, Ph D University of Tennessee, Knoxville *Professor of Nutrition* (2, 1927, 5, 1933)
- MacLeod, Grace, M A, Ph D 106 Morningside Drive New York City *Professor Emeritus of Nutrition Teachers College, Columbia University* (2, 1924, 5, 1933)
- MacLeod, John, M S, Ph D Cornell University Medical College, 1300 York Ave New York City *Assistant Professor of Anatomy* (1, 1942)
- MacNabb, Andrew L, V S, B V Sc, F A P H A Department of Health of Ontario, Toronto, Canada *Director of Laboratories* (6, 1941)
- MacNider, William deB, M D, Sc D, LL D University of North Carolina, Chapel Hill *Kenan Research Professor of Pharmacology, Member, National Academy of Sciences* (1, 1912, 2, 1912, 3, 1909, 4, prior to 1920)
- Macht, David Israel, M D, Phar D (hon), Litt D 3420 Auchentoroly Ter, Baltimore, Md *Research Pharmacologist, Sinai Hospital Labo-*

- atories, and Consultant Pharmacologist, Sinai Hospital* (1, 1916)
- MacPhillamy, Betty Bowser**, M S , Ph D 35 Beekman Rd , Summit, N J *Virologist* (6, 1944)
- Madden, Sidney C**, M D Emory University, School of Medicine, Atlanta, Ga *Professor of Pathology* (4, 1939)
- Maddock, Stephen**, M D Boston City Hospital, Boston, Mass *Director of Surgical Research Laboratory* (4, 1931)
- Madsen, Louis L**, Ph D Dept of Animal Husbandry, Utah State Agricultural College, Logan *Nutritionist* (5, 1940)
- Magath, Thomas B**, M S , Ph D , M D Mayo Clinic, Rochester, Minn *Associate Professor of Clinical Bacteriology and Parasitology, University of Minnesota, Mayo Foundation, Consultant Physician in Clinical Laboratories, Mayo Clinic* (1, 1928)
- Magill, Thomas P**, M D Cornell University Medical College, 1300 York Ave , New York City (6, 1937)
- Magoun, Horace W**, Ph D Northwestern University Medical School, 303 E Chicago Ave , Chicago, Ill *Professor of Microscopic Anatomy* (1, 1937)
- Mahon, Eleanor Conway**, Ph D Iron River, Mich (4, 1940)
- Main, Rolland J**, Ph D Medical College of Virginia, Richmond *Professor of Physiology* (1, 1936)
- Maison, George L**, M S , M D 310 Harris Ave , Needham, Mass (1, 1939)
- Major, Randolph T**, M Sc , Ph D Coles Ave , Mountainside, Westfield, N J *Director of Research, Merck & Co , Inc , Rahway, N J* (2, 1942)
- Mallory, G Kenneth**, M D Mallory Institute of Pathology, Boston City Hospital, Boston, Mass *Professor* (4, 1940)
- Mallory, Tracy B**, M D Massachusetts General Hospital, Boston *Director of Pathology and Bacteriology, Assistant Professor of Pathology, Harvard Medical School* (4, 1937)
- Maloney, Arnold H**, Ph D , M D , LL D Howard University School of Medicine, Washington, D C *Professor and Head of Department of Pharmacology* (3, 1932)
- Maltaner, Frank**, Ph D 388 New Scotland Ave , Albany, N Y *Associate Biochemist, Division of Laboratories and Research, New York State Department of Health* (6, 1920)
- Maluf, N S Rustum**, M S , Ph D Surgical Service, University of Minnesota Hospitals, Minneapolis 14, Minn *Surgical Service* (1, 1942)
- Man, Evelyn B**, Ph D 333 Cedar St , New Haven, Conn *Assistant Professor in the Biochemistry Laboratory, Dept of Psychiatry, Yale University School of Medicine* (2, 1936)
- Manery, Jeanne Forest**, M A , Ph D Medical School, University of Toronto, Toronto, Ont , Canada *Demonstrator in Biochemistry* (1, 1937)
- Mann, Frank C**, M A , M D , Sc D , LL D Mayo Clinic, Box 256, Rochester, Minn *Director, Division of Experimental Medicine, Professor of Experimental Medicine, Mayo Foundation* (1, 1916, 3, 1923, 4, 1921)
- Manning, G W**, M D 20 Woodington Ave , Toronto, Ontario, Canada *Medical Officer in Charge, No 2 R C A F Research Unit* (1, 1944)
- Manville, Ira Albert**, M A , M D , Ph D 811 N W 19th Ave , Portland 9, Ore (1, 1933)
- Manwaring, Wilfred H**, M D Stanford University, Palo Alto, Calif *Professor Emeritus of Bacteriology and Experimental Pathology* (4, prior to 1920, 6, 1917)
- Marine, David**, M A , M D 18 Baltimore Ave , Rehoboth, Del (1, 1910, 4, 1913)
- Markee, Joseph L**, Ph D Duke University School of Medicine, Durham, N C *Professor of Anatomy* (1, 1915)
- Markowitz, J**, M D , Ph D 220 Bloor St , Toronto, Ont , Canada *Research Associate in Physiology, University of Toronto, Faculty of Medicine* (1, 1929)
- Marmont, George H**, Ph D Institute of Radiobiology and Biophysics, University of Chicago, Chicago 37, Ill, *Assistant Professor of Physiology* (1, 1941)
- Marmorston, Jessie** 441 S Beverly Drive Beverly Hills, Calif (6, 1932)
- Marrazzi, Amédeo S**, M D Wayne University College of Medicine, Detroit 26, Mich *Professor and Head of the Department of Pharmacology* (3, 1938)
- Marsh, David F**, A B , M S , Ph D Dept of Pharmacology, West Virginia University, Morgantown, W Va *Head and Associate Professor of Pharmacology* (3, 1946)
- Marsh, Gordon**, Ph D State University of Iowa, Iowa City *Assistant Professor of Zoology* (1, 1944)
- Marsh, M Elizabeth**, M S , Ph D Killian Research Laboratories, 49 W 45th St , New York City *Assistant Director* (1, 1929, 5, 1933)
- Marshak, Alfred George**, M A , Ph D Rockefeller Inst for Med Research, 66th St and York Ave , New York 21, N Y (1, 1940)
- Marshall, Eli Kennerly, Jr**, Ph D , M D , LL D Johns Hopkins Medical School, Baltimore, Md *Professor of Pharmacology and Experimental Therapeutics Member, National Academy of Sciences* (1, 1915, 2, 1913, 3, 1915)

- Marshall, Louise Hanson (Mrs Wade H), A B, M A, Ph D Dept of Physiology, Natl Inst of Health, Bethesda, Md *Assistant Physiologist* (1, 1916)
- Marshall, Wade H, Ph D 9700 Brunett Ave, Silver Spring, Md Wilmer Ophthalmological Institute Johns Hopkins Hospital Baltimore, Md *Associate in Physiological Optics, Johns Hopkins Hospital* (1, 1937)
- Martin, Arthur W, Jr, Ph D 202 Physiology Hall, University of Washington, Seattle *Associate Professor of Animal Biology* (1, 1911)
- Martin, Donald S, M D Duke Hospital, Durham, N C *Associate Professor of Bacteriology and Associate in Medicine, Duke University School of Medicine, Acting Professor of Preventive Medicine and Public Health* (4, 1940, 6, 1943)
- Martin, Stephens J, M A, Ph D St Francis Hospital, Hartford, Conn (1, 1933)
- Mason, Edward C, M D, Ph D University of Oklahoma School of Medicine, Oklahoma City *Professor of Physiology* (1, 1935)
- Mason, H L, M A, Ph D Mayo Clinic, Rochester, Minn *Associate Professor of Physiological Chemistry, The Mayo Foundation, University of Minnesota* (2, 1941)
- Mason, Eleanor Dewey, A B, A M, Ph D Dept of Physiology and Nutrition, Women's Christian College, Cathedral P O, Madras, India *Professor of Physiology and Nutrition* (1, 1946)
- Mason, Karl Ernest, Ph D The University of Rochester, School of Medicine and Dentistry, Rochester, N Y *Professor of Anatomy* (1, 1932, 5, 1941)
- Mason, Morton F, Ph D Parkland Hospital, Oak Lawn Ave, Dallas, Texas *Professor of Pathological Chemistry and Experimental Medicine, Southwestern Medical College* (2, 1938)
- Massengale, Oliver N, Ph D Mead Johnson & Co, Research Laboratory, Evansville, Ind *Research Biochemist* (2, 1937)
- Masson, Georges M C, Ph D McGill University, Montreal, Canada *Research Associate* (1, 1944)
- Mast, S O, Ph D Johns Hopkins University, Baltimore, Md *Professor of Zoology* (1, 1920)
- Mathews, Albert Prescott, Ph D, D Sc (hon) Woods Hole, Mass *Professor Emeritus of Biochemistry, Univ of Cincinnati* (1, 1898, 2, 1906)
- Mattill, Henry A, A M, Ph D State University of Iowa, Iowa City *Professor of Biochemistry* (1, 1913, 2, 1909, 5, 1933)
- Mattis, Paul A, B S, D Sc School of Pharmacy, Univ of Florida, Gainesville, Fla *Head Professor of Pharmacognosy and Pharmacology* (3, 1946)
- Maurer, Frank W, Ph D 301 Lake Ave, Newton Highlands 61, Mass (1, 1911)
- Mautz, Frederick R, M D Western Reserve School of Medicine, Cleveland 6, O *Assistant Professor of Surgery* (1, 1945)
- Mavor, James Watt, Ph D 24 Edward St, Belmont 78, Mass (1, 1930)
- Mayer, Manfred M, Ph D 69 Seversky Court, Baltimore, Md *Instructor in Biochemistry* (6, 1916)
- Mayerson, Hymen S, Ph D Tulane University School of Medicine, Station 20, New Orleans, La *Professor of Physiology and Head of Dept of Physiology* (1, 1929)
- Maynard, Leonard A, Ph D, Sc D Cornell University, Ithaca, N Y *Professor of Nutrition, Director, School of Nutrition, Member National Academy of Sciences* (2, 1930, 5, 1933)
- Mazur, Abraham, M A, Ph D Dept of Medicine, Cornell Univ Medical College, 1300 York Ave, New York 21 N Y *Research Associate* (2, 1944)
- McCann, William S, M D, D Sc (Hon) University of Rochester, School of Medicine, Rochester, N Y *The Charles A Deacy Professor of Medicine* (2, 1923, 5, 1933)
- McCarrell, June D Dept of Physiology, Vassar College, Poughkeepsie, N Y (1, 1942)
- McCawley, Elton Leeman, Ph D Yale Medical School, New Haven, Conn *Instructor in Pharmacology* (3, 1944)
- McCay, Clive M, M S, Ph D Animal Nutrition Laboratory, Dairy Building, Cornell University, Ithaca, N Y *Professor of Nutrition* (2, 1929, 5, 1933)
- McChesney, Evan William, Ph D Sterling-Winthrop Research Institute, 33 Riverside Ave, Rensselaer, N Y *Research Biochemist* (1, 1944)
- McClellan, Walter S, M D Saratoga Spa, Saratoga Springs, N Y *Medical Director, Associate Professor of Medicine, Albany Medical College* (1, 1931)
- McClendon, J F, M S, Ph D Route 1, Box 383, Trooper Road, Norristown, Pa *Research Professor of Physiology, Hahnemann Medical College* (1, 1910, 2, 1914, 5, 1935)
- McClosky, William T, B A 5120 7th St, N W, Washington, D C *Senior Pharmacologist, Div of Pharmacology, Food and Drug Administration* (3, 1929)
- McCollum, Elmer Verner, M A, Ph D, Sc D, LL D Johns Hopkins University, Baltimore, Md *Emeritus Professor of Biochemistry, Member, National Academy of Sciences* (2 1910, 5, 1933)
- McCollum, Ernestine Becker, M A, Johns Hopkins University, School of Hygiene, Baltimore 5,

- Md Assistant Professor of Biochemistry (5, 1938)
- McCouch, Grayson Prevost**, M D University of Pennsylvania, Philadelphia Assistant Professor of Physiology (1, 1925)
- McCrea, Forrest D**, Ph D Duke University School of Medicine, Durham, N C Associate Professor of Physiology and Pharmacology (1, 1929, 3, 1937)
- McCrudden, F H**, M D 501 Boylston St, Boston, Mass Assistant Medical Director, New England Mutual Life Insurance Co (2, 1906)
- McCullagh, D Roy**, M Sc (Man), Ph D (Cantab), FIC 150 Northfield Rd, Bedford, O Vice-President (2, 1932)
- McCulloch, Warren Sturgis**, M A, M D University of Illinois, College of Medicine, 912 S Wood St, Chicago Associate Professor of Psychiatry (1, 1936)
- McCutcheon, Morton**, M D University of Pennsylvania Medical School, Philadelphia Professor of Pathology (4, 1925)
- McDonald, Francis Guy**, M S, Ph D Research Laboratory, Mead Johnson & Co, Evansville, Ind Research Biochemist (2, 1936)
- McElroy, L W** Dept of Animal Science, Uni-Associate Professor of Animal Husbandry (5, 1944)
- McElroy, William D**, Ph D Dept of Biology, Johns Hopkins University, Baltimore, Md (1, 1945)
- McEllroy, William Swindler**, M D School of Medicine, University of Pittsburgh, Pittsburgh, Pa Professor of Physiological Chemistry, Dean, School of Medicine (2, 1919)
- McFarland, Ross A**, Ph D Harvard University, Division of Industrial Research, Graduate School of Business Administration, Soldiers Field, Boston, Mass Assistant Professor of Industrial Research (1, 1943)
- McFarlane, William Douglas**, Ph D Macdonald College, (McGill University), Macdonald College, P Q, Canada Professor of Chemistry (2, 1933)
- McGinty, Daniel A**, M A, Ph D Parke, Davis & Co, Detroit, Mich Research Physiologist (1, 1925)
- McGuigan, Hugh Alister**, Ph D, M D 1853 W Polk St, Chicago, Ill Professor of Pharmacology and Therapeutics, College of Medicine, University of Illinois (1, 1907, 2, 1906, 3, 1913)
- McHargue, J S**, M S, Ph D, D Sc Department of Chemistry, Kentucky Agricultural Experiment Station, University of Kentucky, Lexington Emeritus Member (2, 1927)
- McHenry, E W**, M A, Ph D, F R S C School of Hygiene, University of Toronto, Toronto, Canada Professor of Public Health Nutrition (2, 1938, 5, 1935)
- McIntyre, A R**, Ph D, M D College of Medicine, University of Nebraska, 12nd and Dewey Ave, Omaha Professor of Physiology and Pharmacology (1, 1933, 3, 1938)
- McKee, Clara M**, Squibb Institute for Medical Research, New Brunswick, N J Associate in Microbiology (6, 1911)
- McKee, Ralph Wendell**, M S, Ph D Harvard Medical School, 25 Shattuck St, Boston, Mass Associate, Dept of Biochemistry (2, 1916)
- McLain, Paul L**, M D University of Pittsburgh Medical School, Pittsburgh, Pa Assistant Professor of Physiology and Pharmacology, Major, M C (3, 1910)
- McLean, Franklin C**, Ph D, M D University of Chicago, Chicago, Ill Professor of Pathological Physiology (1, 1911, 2, 1916, 3, 1916)
- McLean, I William, Jr**, B S, M D Virus Research Division, Parke Davis Laboratory, Detroit, Mich Senior Research Associate (6, 1916)
- McLester, James S**, M D, LL D University of Alabama, 930 S 20th St, Birmingham Professor of Medicine (5, 1933)
- McMaster, Philip D**, M D The Rockefeller Institute for Medical Research, 66th St and York Ave, New York City (4, 1921)
- McMeekin, Thomas L**, Ph D Eastern Regional Research Laboratory, U S Department of Agriculture, Philadelphia, Pa Senior Chemist (2, 1935)
- McNaught, James Bernard**, M D University of Colorado School of Medicine, Denver 7 Professor of Pathology (4, 1936)
- McPhail, Murchie Kilburn**, Ph D Dalhousie University, Halifax, Nova Scotia Professor of Pharmacology (3, 1911)
- McQuarrie, Irvine**, Ph D, M D University of Minnesota, Minneapolis Professor and Head of Department of Pediatrics (4, 1927, 5, 1933)
- Medes, Grace**, Ph D Lankenau Hospital Research Institute, Philadelphia, Pa Research Physiological Chemist (2, 1930)
- Medlar, Edgar M**, M D Path Bldg, Room 708 Bellevue Hospital, 1st Ave at 26th St, New York, N Y Pathologist (4, 1927)
- Meek, Walter J**, Ph D University of Wisconsin, Madison Professor of Physiology, Assistant Dean of the Medical School (1, 1908)
- Mehl, John Wilbur**, M A, Ph D Dept of Biochemistry, University of Southern California, Los Angeles Calif Associate Professor (2, 1946)
- Mellon, Ralph R**, M D, M Sc, Dr P H, Sc D (hon) Institute of Pathology, Western Pennsylvania Hospital, Pittsburgh Director (6, 1918)
- Melnick, Daniel**, Ph D Food Research Laboratories, Inc, 48-14 33rd St, Long Island City, N Y Chief Chemist (2, 1940, 5, 1942)

- Melmick, Joseph L., Ph D Yale University School of Medicine, New Haven, Conn Assistant Professor of Preventive Medicine (2, 1916)
- Melville, Kenneth Ivan, M Sc, M D, C M McGill University, Montreal, Canada Assistant Professor of Pharmacology (3, 1931)
- Mendenhall, Walter L., SM, M D Boston University Medical School, 80 E Concord St, Boston, Mass Professor of Pharmacology (1, 1915, 3, 1917)
- Mendez, Rafael, M D Loyola University School of Medicine, 706 S Wolcott Ave, Chicago, Ill Assistant Professor of Pharmacology (3, 1944)
- Meneely, George R., M D Vanderbilt Univ School of Medicine, Nashville 4, Tenn Instructor in Medicine (4, 1916)
- Menkin, Vily, M A, M D Temple Univ School of Medicine, Philadelphia, Pa Associate Professor of Experimental Pathology (1, 1932, 4, 1932, 6, 1931)
- Menten, Maud L., M D, Ph D University of Pittsburgh, Pittsburgh, Pa Associate Professor of Pathology (1, 1915, 4, 1927)
- Mettier, Stacy R., M D University of California Hospital, San Francisco Associate Professor of Medicine (4, 1932)
- Mettler, Fred A., A M, Ph D, M D Department of Neurology, College of Physicians and Surgeons, Columbia University, New York City Associate Professor of Anatomy (1, 1937)
- Meyer, Curtis E., M S, Ph D The Upjohn Co, Kalamazoo, Mich Research Chemist (2, 1942)
- Meyer, Karl, M D, Ph D 630 W 168th St, New York City Associate Professor of Biochemistry, Dept of Ophthalmology, College of Physicians and Surgeons, Columbia University (2, 1934)
- Meyer, Karl F., M D, Ph D Medical Center, San Francisco, Calif Professor of Bacteriology, University of California Director of the George Williams Hooper Foundation for Medical Research (4, 1930, 6, 1922)
- Meyerhof, Otto, M D, LL D Department of Physiological Chemistry, University of Pennsylvania School of Medicine, Philadelphia Research Professor of Biochemistry (2, 1941)
- Michaelis, Leonor, M D, LL D Rockefeller Institute for Medical Research, 66th St and York Ave, New York City Member Emeritus (2, 1929)
- Mickelsen, Olaf, Ph D University of Minnesota, Department of Physiological Hygiene, Stadium South Tower, Minneapolis Assistant Professor (2, 1944)
- Mider, George Burroughs, M D Strong Memorial Hospital, Rochester 7, N Y Research Associate in Surgery (4, 1940)
- Miles, Walter R., A M, Ph D 333 Cedar St, New Haven, Conn Professor of Psychology, The School of Medicine and the Institute of Human Relations, Yale University, Member of the National Academy of Sciences (1, 1919)
- Milhorat, Ade T., M D Cornell University Medical College, 1300 York Ave, New York City Associate Professor of Medicine, Research Fellow, Russell Sage Institute of Pathology (1, 1934, 3, 1937, 5, 1935)
- Miller, Augustus Taylor, Jr, Ph D University of North Carolina Medical School, Chapel Hill Associate Professor of Physiology (1, 1944)
- Miller, Benjamin F., Ch E, M D Dept of Medicine, Univ of Chicago, Chicago, Ill Assistant Professor of Medicine (2, 1938)
- Miller, Carey D., M S University of Hawaii, Honolulu Professor of Food and Nutrition, Hawaii Agricultural Experimental Station (5, 1942)
- Miller, C Phillip, M D, M S University of Chicago, Chicago, Ill Professor of Medicine (4, 1925, 6, 1928)
- Miller, Edgar C L., M D %Library, Medical College of Virginia, Richmond Directing Librarian (6, 1913)
- Miller, Edgar G., Jr, Ph D 630 W 168th St, New York City Professor of Biological Chemistry, Columbia University (2, 1930)
- Miller, Franklin R., M D Jefferson Medical College and Hospital, Division of Hematology, Philadelphia, Pa Associate Professor of Medicine (4, 1940)
- Miller, Frederick R., A M, M D, F R C P (C), F R S Faculty of Medicine, University of Western Ontario, London, Ont, Canada Professor of Physiology (1, 1908)
- Miller, G H., A M, M D American University of Beirut, Beirut, Syria Dean of the College of Medicine (3, 1925)
- Miller, Lila, M S, Ph D Dept of Biological Chemistry, University of Michigan, Ann Arbor, Mich Assistant Professor of Biological Chemistry (2, 1946)
- Miller, Lloyd C., Ph D Sterling-Winthrop Research Institute, 33 Riverside Ave, Rensselaer, N Y Director, Biology Division (3, 1938)
- Miller, R C., Ph D Pennsylvania State College, State College Assistant Professor Agricultural and Biological Chemistry (5, 1935)
- Miller, Zelma Baker, Ph D 2444 Laughlin Ave, La Crescenta, Calif (2, 1940)
- Millikan, Glenn A., Ph D Vanderbilt Univ, Nashville, Tenn (1, 1940)
- Mills, Clarence A., Ph D, M D 228 Woolper Ave, Cincinnati, O Professor of Experimental Medicine, University of Cincinnati (1, 1921, 2, 1921)

- Minot, Annie Stone, Ph D Vanderbilt University Medical School, Nashville, Tenn *Research Associate, Department of Pharmacology* (1, 1923)
- Mirsky, Alfred E., Ph D Rockefeller Inst., 66th St and York Ave., New York 21, N Y *Associate Member* (2, 1941)
- Mirsky, I. Arthur, M Sc, M D, C M The Jewish Hospital, Cincinnati, O *Director, The May Institute for Medical Research, Assistant Professor of Biochemistry, University of Cincinnati* (1, 1936)
- Mitchell, Harold H., M S, M D 120 S Lasky Dr., Beverly Hills, Calif (6, 1913)
- Mitchell, Harold H., M S, Ph D 557 Davenport Hall, University of Illinois, Urbana, Ill *Professor of Animal Nutrition* (2, 1919, 5, 1933)
- Mitchell, Helen S., Ph D Massachusetts State College, Amherst, Mass *Dean of the School of Home Economics* (2, 1925, 5, 1933)
- Mitchell, Philip H., Ph D Brown University Providence 12, R I *Robert P. Brown Professor of Biology* (2, 1909)
- Modell, Walter, M D Cornell University Medical College, 1300 York Ave., New York, N Y *Instructor in Pharmacology* (3, 1944)
- Moe, Gordon Kenneth, Ph D, M D University of Michigan, Ann Arbor *Assistant Professor of Pharmacology* (3, 1944)
- Mohn, James F., M D 24 High St., Buffalo, N Y *Instructor in Bacteriology and Immunology, Univ of Buffalo School of Medicine* (6, 1946)
- Molitor, Hans, M D 50 Lawrence St., Rahway, N J *Director, Merck Institute for Therapeutic Research* (1, 1933, 3, 1942)
- Molomut, Norman, M A, Ph D Biological Labs., 16 Clinton St., Brooklyn 2, N Y (6, 1942)
- Moon, Virgil H., M Sc, M D Jefferson Medical College, Philadelphia, Pa *Professor of Pathology* (4, 1934)
- Moore, A. R., Ph D University of Oregon, Eugene *Research Professor of General Physiology in the Department of Psychology* (1, 1912)
- Moore, Carl Vernon, M D Washington University School of Medicine, St Louis, Mo *Professor of Medicine* (4, 1938, 5, 1941)
- Moore, Lane A., Ph D Division of Nutrition and Physiology, Bureau of Dairy Industry, Beltsville, Md *Head, Section of Dairy Cattle Nutrition* (5, 1940)
- Moore, Robert A., M D Washington University Medical School, St Louis, Mo *Professor of Pathology, Acting Dean* (4, 1929)
- Moore, Robert M., M D 5808 Westminster, St Louis, Mo *Lt Col, M C* (1, 1932)
- Moorhouse, Victor Henry K., M B University of Manitoba, Winnipeg, Canada *Professor of Physiology* (1, 1912)
- Morgan, Agnes Fay, M S, Ph D University of California, Berkeley *Professor of Home Economics, Biochemist, Agric Exp Station, Head, Department of Home Economics* (2, 1929, 5, 1933)
- Morgan, Clifford T., M A, Ph D 105 Mergenthaler Hall, Johns Hopkins University, Baltimore 18, Md (1, 1913)
- Morgulis, Sergius, A M, Ph D University of Nebraska College of Medicine, Omaha *Professor of Biochemistry* (1, 1914, 2, 1916)
- Morison, Robert S., M D Rockefeller Foundation, 66th St and York Ave., New York City *Assist Director of the Med Sciences* (1, 1938)
- Moritz, Alan R., M D Harvard Medical School, Boston, Mass *Professor of Legal Medicine* (4, 1931)
- Morrell, Clarence Allison, M A, Ph D Department of Pensions and National Health, Laboratory of Hygiene, Sussex and John Sts., Ottawa, Canada *Senior Pharmacologist* (3, 1937)
- Morris, Harold P., M S, Ph D National Cancer Institute, Bethesda, Md *Senior Nutrition Chemist, U S Public Health Service* (2, 1944, 5, 1943)
- Morris, Marion C. Public Health Research Institute of City of New York, Foot of East 15th St., New York City *Associate in Division of Infectious Diseases* (6, 1936)
- Morrison, Dempsey B., M S, Ph D University of Tennessee College of Medicine, Memphis *Associate Professor of Chemistry* (2, 1936)
- Morrison, James L., Ph D Emory University School of Medicine, Emory University, Ga *Assistant Professor of Pharmacology* (3, 1944)
- Morse, Minerva, M S, Ph D 5525 Kimbark Ave., Chicago, Ill *Research Associate, Department of Pediatrics, University of Chicago* (2, 1934)
- Morse, Withrow, Ph D 32 Manchester Rd., Eastchester, via Tuckahoe, N Y *Consultant* (2, 1914)
- Mortimer, Bernard, Ph D, M D 406 Buell Ave., Joliet, Illinois, Cook County Hospital, Chicago (1, 1936)
- Morton, John J., M D University of Rochester, School of Medicine and Dentistry, Rochester, N Y *Professor of Surgery* (4, 1927)
- Moulton, C. Robert, M S, Ph D 5602 Dorchester Ave., Chicago 37, Ill (5, 1933)
- Moxon, Alvin L., M S, Ph D College Station, Brookings, S D *Chemist, South Dakota Agricultural Experiment Station* (2, 1944)

- Mover, Carl A, Ph D 6117 Glenrose Ct, Dallas 1, Texas (1, 1913)
- Mudd, Stuart, M A, M D University of Pennsylvania, Philadelphia *Professor of Bacteriology* (1, 1921, 4, 1927, 6, 1927)
- Muehlberger, Clarence W, M S, Ph D State Health Department Laboratories, Lansing, Mich *State Toxicologist* (3, 1928)
- Mueller, J Howard, M S, Ph D 2176 Centre St, W Roxbury, Mass *Professor of Bacteriology and Immunology, Harvard Medical School* (2, 1922, 4, 1927, 6, 1920)
- Mukherji, B, M B, D Sc All-India Institute of Hygiene and Public Health, Calcutta *Director, Biochemical Standardization Laboratory* (3, 1938)
- Mulder, Arthur G, Ph D University of Tennessee College of Medicine, Memphis *Associate Professor of Physiology* (1, 1937)
- Mulinos, M G, M D, Ph D New York Medical College, Flower and Fifth Avenue Hospitals, Fifth Ave and 105th St, New York 29, N Y *Associate Professor of Pharmacology* (3, 1931)
- Mull, James W, Ph D Maternity Hospital, 2065 Adelbert Rd, Cleveland, O *Senior Instructor in Biochemistry in charge of Biochemical Research in Obstetrics, Western Reserve University* (2, 1937)
- Mullin, F J, M S, Ph D University of Chicago, Chicago, Ill *Assistant Professor of Physiology* (1, 1937)
- Munsell, Hazel E, M A, Ph D Nutrition Biochemistry Labs, Dept of Food Technology, Mass Inst of Technology, Cambridge *Research Associate* (5, 1933)
- Muntwyler, Edward, Ph D Long Island College of Medicine, 350 Henry St, Brooklyn, N Y *Professor of Biochemistry* (2, 1931)
- Murlin, John R, A.M, Ph D, Sc D University of Rochester Medical School, 260 Crittenden Blvd, Rochester, N Y *Professor Emeritus of Physiology and Director Emeritus of Department of Vital Economics* (1, 1906, 2, 1908, 5, 1933)
- Murphy, James B, M D Rockefeller Institute for Medical Research, 66th St and York Ave, New York City *Member* (4, prior to 1920)
- Murray, Everitt G D, O B E, BA honors in Natural Science, M A, L M S S A, F R S C McGill University, Montreal, Canada *Professor of Bacteriology and Immunology and Head of the Department, McGill University, Bacteriologist in Chief to the Royal Victoria Hospital, to the Children's Memorial Hospital and to the Alexandra Hospital* (6, 1933)
- Muus, Jytte, Mag Scient (Univ of Copenhagen), Mount Holyoke College, South Hadley, Mass *Associate Professor* (2, 1916)
- Myers, Chester N, Ph D, Sc D 34 Cedar Place, Yonkers 5, N Y *Chief, Division Chemotherapy, N Y Skin and Cancer Hospital, Associate in Dermatology and Syphilology, College of Physicians and Surgeons, Research Chemist, Vanderbilt Clinic, Director, Chemical and Clinical Research, H A Metz Laboratories, Inc* (2, 1922)
- Myers, Victor C, M A, Ph D, Sc D School of Medicine, Western Reserve University, Cleveland, O (1, 1916, 2, 1910, 5, 1933)
- Nachmansohn, David, M D Dept of Neurology, College of Physicians and Surgeons, Columbia University, 630 W 168th St, New York City *Research Associate in Neurology* (1, 1940)
- Nadler, J Ernest, M D, Med D Sc 80 16 Leferts Blvd, Kew Gardens 15, L I, N Y (3, 1910)
- Nahum, Louis N, M D 1142 Chapel St, New Haven, Conn *Assistant Professor of Physiology, Yale University* (1, 1934)
- Najjar, Victor A, M D Dept of Biological Chemistry, Washington Univ School of Medicine, St Louis, Mo (2, 1946)
- Nash, Thomas P, Jr, M A, Ph D 875 Monroe Ave, Memphis, Tenn *Professor of Chemistry, College of Medicine, Dean of School of Biological Sciences, University of Tennessee* (2, 1923)
- Nasset, Edmund S, M S, Ph D University of Rochester, 260 Crittenden Blvd, Rochester, N Y *Associate Professor of Physiology* (1, 1932, 5, 1940)
- Nathanson, Ira T, M S, M D Massachusetts General Hospital, Boston *Instructor in Surgery, Harvard Medical School, Assistant in Surgery, Mass General Hospital* (1, 1943)
- Nathanson, Morris D, M D 658 S Bonnie Brae St, Los Angeles, Calif *Associate Clinical Professor of Medicine, University of Southern California School of Medicine* (3, 1940)
- Necheles, Heinrich, M D, Ph D Michael Reese Hospital, Chicago, Ill *Director, Dept of Gastro-intestinal Physiology, Michael Reese Hospital, Professorial Lecturer in Physiology, University of Chicago* (1, 1929)
- Neill, James M, Ph D Medical College, Cornell University, 1300 York Ave, New York City *Professor of Bacteriology and Immunology* (6, 1930)
- Neilson, Charles Hugh A M, Ph D, M D Humboldt Building, St Louis, Mo *Associate Dean and Professor of Medicine, St Louis University Medical School* (2, 1906)
- Nelson, Arthur A, M D, Ph D Food and Drug Administration, Federal Security Agency, Wash-

- ington, D C *Senior Pathologist, Division of Pharmacology* (4, 1912)
- Nelson, Carl Ferdinand, M D , Ph D Department of Biochemistry, University of Kansas, Lawrence *Professor of Physiological Chemistry* (2, 1914)
- Nelson, Carl T , A B , M A , M D College of Physicians and Surgeons, 630 West 168th St , New York 32, N Y *Instructor in Dermatology* (6, 1943)
- Nelson, Erwin E , Ph D , M D Drug Division Food & Drug Administration, Washington 25, D C (1, 1923, 3, 1921)
- Nelson, E M , M S , Ph D Food and Drug Administration, Federal Security Agency, Washington 25, D C *Chief, Vitamin Division* (2, 1927, 5, 1933)
- Nelson, John B , Ph D Rockefeller Institute for Medical Research, Princeton, N J *Associate Member Technical Civilian Aide in India* (1, 1934)
- Nelson, John M , Ph D Columbia University, New York City *Professor of Organic Chemistry* (2, 1923)
- Nelson, Norton, Ph D Childrens Hospital Research Foundation, Elland and Bethesda Avenues, Cincinnati 29, Ohio *Associate, Dept of Biological Chemistry, Medical College, Univ of Cincinnati* (2, 1946)
- Nelson, P Mabel, M S , Ph D Iowa State College, Ames *Dean, Division of Home Economics* (5, 1934)
- Nelson, Tell, M A , M D Kula Sanitarium, Wailua, Maui, Hawaii, T H (6, 1938)
- Nelson, Victor E , M S Iowa State College, Ames *Professor of Physiological Chemistry* (2, 1924)
- Nelson, Warren O , M S , Ph D Dept of Anatomy, School of Medicine, Univ of Iowa, Iowa City *Professor of Anatomy* (1, 1937)
- Neter, Erwin, M D Children's Hospital, 219 Bryant St , Buffalo, N Y *Attending Bacteriologist* (6, 1937)
- Nettleship, Anderson, M D Alexander Blain Hospital, 2201 Jefferson East, Detroit, Mich *Director* (4, 1942)
- Neuberg, Carl, Ph D , M D (h c), Med Chem D (h c), Biol D (h c), Dr Eng (h c), LL D 536 W 113th St , New York 25, N Y *Research Professor, New York University, Member or hon member of the Academies of Science of Copenhagen, Göttingen, Leningrad, Lisbon, Lund, Prag, Rome and Upsala* (2, 1944)
- Neumann, Charles, M D 525 East 68th Street, New York 21, N Y *Resident Surgeon, New York Hospital, Instructor in Surgery, Cornell University Medical College* (1, 1944)
- Neurath, Hans, Ph D School of Medicine, Duke University, Durham, N C *Associate Professor of Biochemistry* (2, 1910, 6, 1911)
- Neuwelt, Frank, M D 501 Broadway, Gary, Ind *Research Associate, Department of Gastrointestinal Research, Michael Reese Hospital* (1, 1910)
- Neuwirth, Isaac, Ph D 209 E 23rd St , New York City *Associate Professor of Pharmacology and Therapeutics, New York University College of Dentistry* (2, 1921, 3, 1931)
- Nice, Leonard B , Ph D Chicago Medical School, 710 S Wolcott Ave , Chicago, Ill *Professor of Physiology and Pharmacology* (1, 1921)
- Nicholas, John S , M S , Ph D Osborn Zoological Laboratory, Yale University, New Haven, Conn *Bronson Professor of Comparative Anatomy* (1, 1927)
- Nicholson, Hayden C , M S , M D Division of Medical Sciences, National Research Council, 2101 Constitution Ave , Washington 25, D C (1, 1932)
- Nickerson, John L , Ph D Columbia University, 630 W 168th St , New York 32, N Y *Assistant Professor of Physiology* (1, 1915)
- Nicolet, Ben H , Ph D Bureau of Dury Industry, U S Department of Agriculture, Beltsville, Md *Senior Chemist* (2, 1932)
- Nicoll, Paul A , Ph D Indiana University, Bloomington *Assistant Professor of Physiology* (1, 1915)
- Niemann, Carl G , Ph D California Institute of Technology, Pasadena 4, Calif *Professor, Organic Chemistry* (2, 1940)
- Nigg, Clara, M A , Ph D c/o E R Squibb & Sons, New Brunswick, N J (6, 1929)
- Nims, Leslie F , M A , Ph D Yale University School of Medicine, 333 Cedar St , New Haven, Conn *Assistant Professor of Physiology* (1, 1940)
- Noble, Robert Laing, M D , Ph D Research Institute of Endocrinology, McGill University, Montreal, Canada *Research Assistant* (1, 1941)
- Nord, F F , Ph D Fordham University, Dept of Organic Chemistry, New York City *Professor of Chemistry* (2, 1940)
- Norris, Earl R , Ph D University of Washington, Seattle *Professor of Chemistry* (2, 1938)
- Norris, L C , Ph D Rice Hall, Cornell University, Ithaca, N Y *Professor of Nutrition, Secretary, School of Nutrition* (2, 1939, 5, 1934)
- Northrop, J H , M A , Ph D , Sc D , LL D Rockefeller Institute for Medical Research, Princeton, N J *Member* (2, 1938)
- Northup, David W , M A , Ph D West Virginia University Medical School, Morgantown *Associate Professor of Physiology* (1, 1936)
- Novy, F G , M D , Sc D , LL D 721 Forest Ave , Ann Arbor, Mich *Dean Emeritus of the*

- Medical School and Professor Emeritus of Bacteriology, University of Michigan, Member, National Academy of Sciences (2, 1906)
- McC, Robert N, M D S S M W, Boston 18, Mass, Managing Editor, New England Journal of Medicine (6, 1923)
- Oberst, Fred W, M S, Ph D The Wm S Merrell Co, Lockland Station, Cincinnati, O Chief, Division of Biochemistry (2, 1936)
- Ochoa, Severo, M D New York University College of Medicine, 477 First Ave, New York City 16 Professor of Pharmacology (2, 1912)
- Ogden, Eric, M R C S (England), L R C P (London) University of Texas School of Medicine, Galveston Professor of Physiology and Clinical Physiologist, John Sealy Hospital (1, 1941)
- O'Hare, James P, M D 520 Commonwealth Ave, Boston, Mass Physician, Peter Bent Brigham Hospital, Assistant Professor of Medicine, Harvard Medical School (4, 1927)
- Ohlson, Margaret A, M S, Ph D Dept of Foods and Nutrition, Michigan State College, East Lansing Professor and Head, Department of Foods and Nutrition (5, 1945)
- Okey, Ruth, Ph D 1583 Life Sciences Bldg, University of California, Berkeley Professor of Home Economics and Biochemist, State Exp Station (2, 1922, 5, 1933)
- Olcott, Harold S, M S, Ph D Western Regional Research Laboratory, U S Department of Agriculture, Albany 6, Calif Senior Chemist (2, 1935)
- Oldham, Helen, M S, Ph D University of Chicago, Chicago, Ill Assistant Professor, Dept of Home Economics (5, 1946)
- Olitsky, Peter K, M D Rockefeller Institute for Medical Research, 66th St and York Ave, New York City Member (4, 1923, 6, 1917)
- Oliver, Jean Redman, M D Hoagland Laboratory, 335 Henry St, Brooklyn, N Y Professor of Pathology, Long Island College of Medicine (1, 1924, 4, 1924)
- Oliver, Wade W, M D Hoagland Laboratory, 335 Henry St, Brooklyn N Y Professor of Bacteriology, Long Island College of Medicine (4, 1925)
- Olmsted, J M D, M A, Ph D University of California, Berkeley Professor of Physiology (1, 1920)
- Olson, Carl, Jr, D V M, Ph D Univ of Nebraska, Lincoln, Nebr Chairman, Dept of Animal Pathology and Hygiene (4, 1937)
- Opdyke, David F, Ph D Western Reserve Medical School, Cleveland 6, O Senior Instructor in Physiology (1, 1945)
- Ope, Eugene L, M D, Sc D, LL D Rockefeller Institute for Medical Research, 66th St and York Ave, New York 21, N Y Member, National Academy of Sciences (1, 1906, 4, 1913, 6, 1923)
- Oppenheimer, Enid Tribe 124 E 61st St, New York City Instructor in Physiology, Columbia University (1, 1932)
- Oppenheimer, Ernst, M D Ciba Pharmaceutical Products, Inc, Lafayette Park, Summit, N J Vice-President in charge of Medical Research (3, 1941)
- Oppenheimer, Morton Joseph, Ed M, M D 3400 N Broad St, Philadelphia, Pa Associate Professor of Physiology, Temple University School of Medicine (1, 1912)
- Orent-Keiles, Elsa, D Sc Bureau of Human Nutrition and Home Economics, U S Department of Agriculture, Beltsville, Md In Charge of Nutrition Investigations, Assistant Chief, Foods and Nutrition Division (2, 1935, 5, 1935)
- Orl, John M, Ph D 101 Codwise Ave, New Brunswick, N J Director of Research, Carroll Dunham Smith Pharmacal Co (2, 1932)
- Orten, Aline Underhill, M S Ph D Wayne Univ College of Medicine, Detroit 26, Mich Research Associate, Dept of Physiological Chemistry (5, 1946)
- Orten, James M, M S, Ph D Wayne University College of Medicine Detroit Mich Associate Professor of Physiological Chemistry (2, 1936, 5, 1937)
- Orth, O Sidney, M S, Ph D, M D University of Wisconsin Medical School, Madison Associate Professor of Pharmacology (1, 1942, 3, 1944)
- Osborne, Stafford L, B P E, M S, Ph D Northwestern University Medical School, 303 E Chicago Ave, Chicago, Ill Associate Professor of Physical Therapy (1, 1941)
- Oser, Bernard L, M S, Ph D Food Research Laboratories, Inc, 48 14 Thirtieth St, Long Island City 1, N Y Director (5, 1945)
- Oster, Robert H, Ph D University of Maryland Medical School, Greene and Lombard Sts, Baltimore Assistant Professor of Physiology (1, 1938)
- Osterberg, Arnold E, M S, Ph D Medical Dept Abbott Laboratories, No Chicago, Ill Associate in Medical Dept (2, 1933)
- Osterhout, Marian I Rockefeller Institute for Medical Research, 66th St and York Ave, New York City 21 Associate, Division of General Physiology (1, 1927)
- Osterhout, W J V, Ph D Rockefeller Institute, 66th St and York Ave, New York City Member Emeritus of the Institute, Member of the National Academy of Sciences (1, 1910)
- Otis, Arthur B, A B, Sc M, Ph D Dept of Physiology, Univ of Rochester, Rochester 7, N Y Instructor (1, 1946)

- Overman, Richard R , B A , M A , Ph D Dept of Physiology, Univ of Tennessee, Memphis, Tenn *Instructor* (1, 1916)
- Owen, Seward E , M S , Ph D 418 So 20th Ave , Maywood, Ill *Major, S E Sn Corps* (1, 1938)
- Pace, Donald M , Ph D Dept of Physiology and Pharmacology, College of Pharmacy, University of Nebraska, Lincoln *Associate Professor of Physiology* (1, 1944)
- Pack, George T , M D 139 E 36th St , New York City 16 *Fellow in Cancer Research, Memorial Hospital* (1, 1924)
- Packchianian, Ardzoony, Ph D School of Medicine, University of Texas, Galveston *Associate Professor of Bacteriology and Tropical Medicine, and Director of Laboratory of Microbiology* (6, 1943)
- Page, Irvine H , M D Cleveland Clinic Foundation, Euclid Ave and 93rd St , Cleveland 6, O *Director of Research Division* (1, 1937, 2, 1932)
- Painter, Elizabeth E , Ph D Loyola Univ School of Medicine, 706 S Wolcott, Chicago 12, Ill *Assistant Professor of Pharmacology* (1, 1941)
- P'An, S Y , M D Peiping Union Medical College, Peiping, China *Assistant in Pharmacology* (3, 1941)
- Pangborn, Mary C , Ph D 20 Morris St , Albany, N Y *Senior Biochemist, New York State Department of Health, Division of Laboratories and Research* (2, 1941)
- Pappenheimer, Alwin M , Jr , Ph D New York Univ College of Medicine, 477 First Ave , New York 16, N Y *Assistant Professor* (2, 1941, 6, 1938)
- Pappenheimer, Alwin M , M D 5 Acacia St , Cambridge, Mass *Professor Emeritus of Pathology, Columbia University* (4, 1922)
- Pappenheimer, John R , B S , Ph D Harvard Medical School, Boston, Mass *Associate in Physiology* (1, 1946)
- Park Edwards A M D Johns Hopkins Hospital, Baltimore, Md *Emeritus Professor of Pediatrics, Johns Hopkins University* (4, 1923)
- Parker, George Howard, Sc D 16 Berkeley St , Cambridge, Mass *Professor of Zoology Emeritus, Harvard University, Member of the National Academy of Sciences* (1, 1900)
- Parker, Robert F , M D Lakeside Hospital, 2065 Adelbert Rd , Cleveland, O *Associate Professor of Medicine* (4, 1942, 6, 1935)
- Parkins, William M , M A , Ph D School of Medicine, University of Pennsylvania, Philadelphia *Research Associate, Harrison Department of Surgical Research* (1, 1939)
- Parrpart, Arthur K , Ph D Guyot Hall, Princeton University, Princeton, N J *Associate Professor of Physiology* (1, 1937)
- Parr, Leland W , Ph D The George Washington University School of Medicine, 1335 H St , N W Washington, D C *Professor of Bacteriology* (4, 1910)
- Parsons, Helen T , M S , Ph D University of Wisconsin, Madison *Professor of Home Economics, In Charge of Purnell Research in Nutrition* (2, 1929, 5, 1933)
- Parsons, Robert J , M D Alameda County Institution, 2701 14th Ave , Oakland, Calif *Pathologist and Director of Laboratories* (4, 1939)
- Paschke, Karl E , M D 1025 Walnut St , Philadelphia, Pa *Chief of Clinic, Endocrine Clinic, Associate in Physiology, Associate in Medicine, Jefferson Medical College and Hospital* (1, 1912)
- Patterson, Thos L , A M , M S , Ph D , Sc D (hon) Wayne University College of Medicine, 1512 St Antoine St , Detroit, Mich *Research Professor of Physiology* (1, 1920)
- Paul, John R , M D , A M 330 Cedar St , New Haven, Conn *Professor of Preventive Medicine, Yale University Medical School* (4, 1927, 6, 1937)
- Pearce, John Musser, M D Long Island College of Medicine, Hougland Laboratory, 335 Henry St , Brooklyn, N Y *Associate Professor of Pathology* (4, 1912)
- Pearce, Louise, M D Rockefeller Institute for Medical Research, Princeton, N J *Associate Member in Pathology and Bacteriology* (3, 1915, 4, 1925)
- Pearcy, J Frank, Ph D , M D 171 Park Ave , New York City (1, 1928)
- Pearlman, William Henry, Ph D Jefferson Medical College, 1025 Walnut St , Philadelphia 7, Pa *Research Associate* (2, 1916)
- Pearse, Herman E , M D School of Medicine and Dentistry, University of Rochester, Crittenden Blvd , Rochester, N Y *Associate Professor of Surgery* (4, 1932)
- Pearson, Paul B , Ph D A & M College of Texas, College Station *Professor of Nutrition, Nutritionist, Agricultural Experiment Station* (2, 1944, 5, 1940)
- Pease, Marshall C , Jr , M D Branchville Rd , R F D 4, Ridgefield, Conn (6, 1920)
- Pemberton, Ralph, M S , M D University of Pennsylvania, Philadelphia *Professor of Medicine, Graduate School of Medicine* (5, 1933)
- Penfield, Wilder G , M D , D Sc McGill University, Montreal, Que , Canada *Professor of Neurology and Neurosurgery* (1, 1932)
- Pennington, Mary Engle, Ph D 233 Broadway, New York 7, N Y *Consultant in Connection with the Handling, Transportation and Storage of Perishables* (2, 1908)
- Penrod, Kenneth E , B S , Ph D Boston Univ School of Medicine, Dept of Physiology, 80 E

ALPHABETICAL LIST OF ALL MEMBERS OF THE SIX SOCIETIES

- Concord St, Boston, Mass Assistant Professor of Physiology (1, 1916)
- Peoples, S Anderson, M D Baylor University College of Medicine, Houston, Texas Professor of Pharmacology (3, 1937)
- Perlman, Liv, A B, M D Mt Sinai Hospital, 100th St and 11th Ave, New York 29, N Y Research Fellow (6, 1911)
- Perlzweig, William A, A M, Ph D Box 3711, Duke Hospital, Durham, N C Professor of Biochemistry, Duke University, Biochemist Duke Hospital (2, 1924, 5, 1911)
- Permar, Howard H, M D Pathologic Laboratories, Mercy Hospital, Pittsburgh, Pa Director of Laboratories (4, 1925)
- Peters, John P, M D 123 Marvel Road, New Haven 15, Conn Sterling Professor of Medicine, Yale University (2, 1922)
- Peters, Lawrence, B S, Ph D Dept of Pharmacy, Western Reserve Univ Medical School, 2109 Adelbert Rd, Cleveland 6, Ohio Senior Instructor in Pharmacology (3, 1946)
- Petersen, William F, M D 1322 Astor St, Chicago, Ill Professor of Pathology, University of Illinois Director Clinical Research, St Luke's Hospital (3, 1923, 1, 1923)
- Peterson, William H, A M, Ph D Biochemistry Building, University of Wisconsin, Madison Professor of Biochemistry (2, 1919, 5, 1936)
- Petroff, S A, Ph D, Sc D Sea View Hospital, West New Brighton, Staten Island, N Y Director of Bacteriology and Immunology (6, 1926)
- Pett, L B, M D, Ph D Department of National Health and Welfare, Ottawa, Canada Director of Nutrition (2, 1937, 5, 1945)
- Peugnet, Hubert B, M D Department of Surgery, University of Chicago, Chicago, Ill (1, 1938)
- Pfeiffer Carl C, Ph D, M D Department of Pharmacology, University of Illinois, 1853 West Polk St, Chicago 12 Professor of Pharmacology and Chairman of Dept (3, 1938)
- Pfaffner, Joseph J, Ph D Research Laboratories, Parke, Davis & Co, Detroit 32, Mich Research Chemist (1, 1931, 2, 1931, 5, 1946)
- Phatak, Nilkanth M, M S, Ph D North Pacific College of Oregon, School of Dentistry, Portland Associate Professor of Physiology, Pharmacology, and Research and Instructor Dept of Pharmacology, University of Oregon (3, 1941)
- Phillips, Paul H, Ph D University of Wisconsin, Portland Captain, Sn C (3, 1941)
- Phillips, Robert Allan, M D Rockefeller Institute for Medical Research, New York City Fellow (1, 1938)
- Pick, Ernst Peter, M D 19 E 98th St, New York City Associate Pharmacologist to the Mt Sinai Hospital, Clinical Professor of Pharmacology in Columbia University (3, 1940)
- Pierce, Harold B, M S, Ph D College of Medicine, University of Vermont, Burlington Professor and Chairman, Dept of Biochemistry (2, 1929, 5, 1933)
- Pierce, Harold Fisher, Ph D, M D 156 Raymond Rd, West Hartford, Conn Major, MC (1, 1928)
- Pierce, Ira H, M S, Ph D Univ of Iowa, Iowa City Associate Professor of Pharmacology (3, 1933)
- Pike, Frank H, Ph D 137 W 59th St, New York City 19 Associate Professor of Physiology, Columbia University (1, 1907)
- Pilcher, J Douglas, M D City Hospital, Scranton Road, Cleveland, O Associate Professor of Pediatrics, Western Reserve Medical School (1, 1912, 3, 1911)
- Pillemer, Louis, Ph D Inst of Pathology, Western Reserve Univ, Cleveland, O (6, 1942)
- Pincus, Gregory, M S, Sc D Worcester Foundation for Experimental Biology, 222 Maple Ave, Shrewsbury, Mass (1, 1935)
- Pinkerton, Henry, M D St Louis University School of Medicine, St Louis, Mo Professor of Pathology (4, 1931)
- Pinkston, James O, Ph D American University of Beirut, Beirut, Lebanon, Syria Pharmacologist (1, 1936, 3, 1939)
- Pinson, Ernest A, Ph D Biophysics Branch, Aeromedical Laboratory, Wright Field, Dayton, O Major, Air Corps (1, 1943)
- Pittman, Martha S, A M, Ph D Kansas State College, Manhattan Head of Department of Food Economics and Nutrition (5, 1933)
- Pitts, Robert F, Ph D, M D Syracuse Univ College of Medicine, Syracuse, N Y Professor of Physiology and Head of the Department of Physiology (1, 1934)
- Plass, Everett D, M D University Hospital Iowa City, Iowa Professor and Head of Department of Obstetrics and Gynecology, State University of Iowa (2, 1922)
- Plotz, Harry, M D Army Medical Center, Army Medical School, Washington, D C Colonel, Chief of the Division of Virus and Rickettsial Diseases, Chief of Service, Pasteur Institute, Paris, France (6, 1917)
- Pohlman, Augustus G, M D 4056 Farmouth Dr, Los Angeles, Calif Associate Clinical Professor, Department of Otolaryngology, University of Southern California School of Medicine (1, 1934)
- Pollack, Herbert, Ph D, M D 45 E 66th St, New York City 21 Associate Physician and Chief of Metabolism Clinics, Mt Sinai Hospital (1, 1933, 5, 1935)

- Pomerat, Charles Marc**, Ph D University of Texas Medical School, Galveston *Professor of Anatomy* (1, 1944)
- Pond, Samuel E**, A M, Ph D 400 S Main St, East Hartford, Conn *Consulting Engineer, P and W A Division, United Aircraft Corp* (1, 1924)
- Ponder, Eric**, M D, Sc D The Nassau Hospital, Mineola, Long Island, N Y (1, 1931)
- Popper, Hans**, Ph D, M D University of Illinois College of Medicine, 1825 W Harrison St, Chicago *Director of Laboratories and of the Hectoten Institute for Medical Research of Cook County Hospital* (4, 1942)
- Porter, Eugene L**, A M, Ph D University of Texas, Medical Branch, Galveston *Professor of Physiology* (1, 1913)
- Porter, Thelma**, Ph D University of Chicago, Chicago, Ill *Prof and Head of Department of Home Economics* (5, 1914)
- Porter, William Townsend**, M D, Sc D, LL D Dover, Mass *Professor Emeritus of Comparative Physiology, Harvard University* (1, 1891)
- Poth, Edgar J**, M D Univ of Texas Med School Galveston, Texas *Professor of Surgery* (1, 1946)
- Potter, Truman S**, M D 82 N Prospect St, Amherst, Mass (6, 1939)
- Potter, Van Rensselaer**, M S, Ph D McArdle Memorial Laboratory, University of Wisconsin Medical School, Madison *Associate Professor of Oncology* (2, 1941)
- Povitzky, Olga R**, M D, D P H 235 E 22nd St, New York City *Bacteriologist, Bureau of Laboratories, New York City Department of Health* (6, 1920)
- Powell, Horace M**, Sc D 5565 Washington Blvd, Indianapolis, Ind *Bacteriologist, Eli Lilly & Co* (6, 1934)
- Power, Marschelle H**, M S, Ph D Mayo Clinic, Rochester, Minn *Associate Professor of Physiological Chemistry, Mayo Foundation, University of Minnesota* (2, 1932)
- Pratt, Frederick H**, A M, M D Wellesley Hills 82, Mass *Professor of Physiology, Emeritus, Boston University School of Medicine* (1, 1919)
- Pratt, Joseph H**, A M, M D Sc D New England Medical Center, 25 Bennet St, Boston, Mass *Physician-in-Chief, Boston Dispensary, and Joseph H Pratt Diagnostic Clinic, Professor of Clinical Medicine, Tufts Medical School* (1, 1910, 3, 1910, 4, 1927)
- Preisler, Paul W**, M S, Ph D 4274 Shenandoah Ave, St Louis 10, Mo *Assistant Professor of Biochemistry, Washington University Medical School* (2, 1931)
- Prinzmetal, Myron**, M A, M D 2007 Wilshire Blvd, Los Angeles, Calif *Instructor in Medicine and Lecturer in Physiology, University of Southern California Medical School* (3, 1941)
- Prosser, C Ladd**, Ph D Metallurgical Laboratory, University of Chicago, Chicago, Ill (1, 1935)
- Pucher, George W**, Ph D Connecticut Agricultural Experiment Station, New Haven *Research Associate* (2, 1927)
- Puestow, Charles B**, M D, M S, Ph D University of Illinois, College of Medicine, 185 W Polk St, Chicago *Assistant Professor of Surgery Lt Col (MC) AUS* (1, 1931)
- Pugsley, Leonard I**, M Sc, Ph D Laboratory of Hygiene, Department of National Health and Welfare, Ottawa, Canada *Pharmacologist* (2, 1937)
- Quackenbush, Forrest W**, Ph D 213 Connolly St, W Lafayette, Ind *Professor and Head of Dept of Agricultural Chemistry, Purdue Univ* (2, 1916)
- Queen, Frank B**, M D Univ of Oregon School of Medicine, 3181 S W Marquam Hill Rd, Portland, Oregon (1, 1911)
- Quick, Armand J**, M D, Ph D 561 N 15th St, Milwaukee 3, Wis *Professor of Biochemistry and Director of Department, Marquette Medical School* (2, 1932, 3, 1937)
- Quigley, J P**, M S, Ph D Dept of Pharmacology, Univ of Tenn, Memphis 3, Tenn *Professor and Chief of the Division of Physiology and Pharmacology* (1, 1929, 3, 1945)
- Quinby, William Carter**, M D Peter Bent Brigham Hospital, Boston, Mass *Clinical Professor of Genito-urinary Surgery, Harvard Medical School* (1, 1916)
- Quinn, Edmond John**, Ph D 106 N Lee Ave, Rockville Center, Long Island, N Y *Medical Sales Division, Merck & Co, Inc, Rahway, N J* (2, 1927, 5, 1933)
- Rabinowitch, I M**, O B E, D Sc, M D, C M, F R C P, F A C P 1020 Medical Arts Bldg, Sherbrooke and Guy Sts, Montreal 25, Canada *Associate Professor of Medicine and Lecturer in Medical Jurisprudence and Toxicology, McGill University, Director, Department of Metabolism, Montreal General Hospital* (2, 1928, 5, 1933)
- Rackemann, Francis M**, M D 263 Beacon St, Boston, Mass *Physician, Massachusetts General Hospital, Lecturer in Medicine, Harvard Medical School* (6, 1923)
- Raffel, Sidney**, Sc D, M D Department of Bacteriology and Experimental Pathology, Stanford University, Calif *Assistant Professor* (6, 1938)
- Rahn, Hermann**, Ph D University of Rochester School of Medicine and Dentistry, Rochester, N Y *Instructor in Physiology* (1, 1944)
- Rake, Geoffrey W**, M B, M R C S, L R C P Division of Microbiology, The Squibb Institute

- for Medical Research, New Brunswick, N J
Head, Division of Microbiology (6, 1939)
- Lakestraw, Norris W., A M, Ph D Brown
 University, Providence, R I *Professor of*
Chemistry (2, 1925)
- Lakielen, Nathan, Ph D Cheplin Laboratories,
 Inc, P O Box 657, Syracuse 2, N Y *Phar-*
macologist and Toxicologist (1, 1911)
- Lalli, Elaine P., M D 477 First Ave, New York
 City *Associate Professor of Medicine, New*
York University College of Medicine (1, 1934,
 5, 1933)
- Rammelkamp, Charles H., Jr, B A, M D Dept
 of Preventive Medicine, Western Reserve Univ,
 Cleveland 6, Ohio *Assistant Professor of Medi-*
cine (6, 1943)
- Ramsey, Robert Weberg, M S, Ph D Medical
 College of Virginia, Richmond *Associate Pro-*
fessor of Physiology and Pharmacology (1,
 1939)
- Randall, Lowell O., Ph D Burroughs Wellcome
 Co, Tuckahoe, N Y *Pharmacologist* (2, 1939)
- Randall, Walter C., M S, Ph D St Louis Uni-
 versity, School of Medicine, 1402 S Grand Blvd,
 St Louis, Mo *Instructor in Physiology* (1, 1943)
- Randall, William A., B S, M S, Ph D Food and
 Drug Administration, Washington 25, D C
Bacteriologist, Division of Penicillin Control and
Immunology (6, 1946)
- Rane, Leo, Ph D Lederle Laboratories, Inc,
 Pearl River, N Y *Department Head, Normal*
Blood Plasma (6, 1942)
- Rantz, Lowell A., A B, M D Stanford Univ
 Hospital, San Francisco 15, Calif *Assistant Pro-*
fessor of Medicine (3, 1946)
- Rapoport, Samuel, M D, Ph D The Children's
 Hospital Research Foundation, Elland and
 Bethesda, Cincinnati, O *Research Associate*
 (2, 1941)
- Rapport, David, M D 416 Huntington Ave,
 Boston, Mass *Professor of Physiology, Tufts*
College Medical School (1, 1922)
- Rasmussen, Andrew Theodore, Ph D Univer-
 sity of Minnesota Medical School, Minneapolis
Professor of Neurology (1, 1919)
- Ratner, Bret, M D 50 E 78th St, New York
 City *Professor of Pediatrics, New York Univ*
College of Medicine (4, 1940, 6, 1928)
- Ratner, Sarah, Ph D Dept of Pharmacology,
 N Y Univ College of Medicine, 477 First Ave,
 New York 16, N Y (2, 1944)
- Raulston, B O., A B, M D 200 S Hudson Ave,
 Los Angeles, Calif *Professor of Medicine, Direc-*
tor of Clinical Teaching, and Associate Dean, the
University of Southern California, School of
Medicine (3, 1942)
- Raydin, I S, M D University of Pennsylvania
 School of Medicine, Philadelphia John Rea
 Barton *Professor of Surgery, Chief Surgeon,*
Hospital of the University of Pennsylvania (1,
 1930, 4, 1930)
- Raymond, Albert L., Ph D G D Searle & Co,
 P O Box 5110, Chicago 80, Ill *Director of Re-*
search (2, 1932)
- Reback, John F., B S, M S 317 E Duval Ave,
 South Bend 14, Ind *Bacteriologist, 4th General*
Hospital, A U S (6, 1943)
- Redfield, Alfred C., Ph D Woods Hole, Mass
Professor of Physiology, Harvard University
 (1, 1919)
- Reed, Carlos Isaac, A M, Ph D College of
 Medicine, University of Illinois, 1853 W Polk
 St, Chicago *Professor of Physiology* (1,
 1923)
- Reed, Howard S., Ph D 3048 Life Sciences
 Bldg, University of California, Berkeley
Professor of Plant Physiology (2, 1909)
- Rehm, Warren S., Jr, Ph D, M D University
 of Louisville School of Medicine, Louisville, Ky
Assistant Professor of Physiology (1, 1945)
- Reid, Marion Adelaide, A M, Ph D 80 E
 Concord St, Boston, Mass *Instructor in*
Physiology, Boston University (1, 1941)
- Reimann, Hobart A., M D Jefferson Hospital,
 Philadelphia, Pa *Professor of Medicine, Jef-*
erson Medical College (4, 1933)
- Reimann, Stanley P., M D, Sc D 703 W Phil-
 ellena St, Mount Airy, Philadelphia, Pa
Director of the Research Institute of the Lankenau
Hospital, Director, Institute of Cancer Research
Associate Professor of Surgical Pathology,
Graduate School of Medicine, University of
Pennsylvania, Professor of Oncology, Hahne-
mann Medical College and Hospital, Philadel-
phia (1, 1921, 4, 1924)
- Reiner, Laszlo, M D, Ph D 165 Franklin St,
 Bloomfield, N J *Research Department, Wallace*
& Tiernan Company (2, 1942, 6, 1933)
- Reinhold, John G., M S, Ph D Philadelphia
 General Hospital, 34th St and Curie Ave,
 Philadelphia, Pa *Principal Biochemist, In-*
structor in Physiological Chemistry, University of
Pennsylvania (2, 1936)
- Remington, John W., M S, Ph D University of
 Georgia, School of Medicine, Augusta *Assistant*
Professor of Physiology (1, 1943)
- Remington, Roe E., M A, Ph D, D Sc Hender-
 sonville, N C *Consultant* (2, 1930, 5, 1934)
- Renfrew, Alice G., Ph D Mellon Institute of
 Industrial Research, University of Pittsburgh,
 Pittsburgh, Pa *Fellow, Department of Research*
in Pure Chemistry (2, 1939)
- Renshaw, Birdsey, M A, Ph D Oberlin College,
 Oberlin, O *Assistant Professor of Physiology*
 (1, 1941)
- Reynolds, Chapman, M D Louisiana State Uni-
 versity, School of Medicine, New Orleans *Assist-*
ant Professor of Pharmacology (3, 1937)

- Reynolds, Samuel R M**, Ph D 4028 Dupwood Rd, Baltimore 18, Md *Carnegie Institution of Washington, Major, A L S* (1, 1932)
- Reznikoff, Paul**, M D New York Hospital, 525 E 68th St, New York City *Associate Professor of Clinical Medicine, Cornell University Medical College* (1, 1927)
- Rhoads, Cornelius Packard**, M D Memorial Hospital, 444 E 68th St, New York City *Director, Professor of Pathology, Cornell University Medical College, Director of Sloan-Kettering Institute for Cancer Research* (4, 1930)
- Rhoads, Jonathan Evans**, B A, M D, D Sc 1023 Pine St, Philadelphia 4, Pa *Assistant Professor of Surgical Research* (1, 1946)
- Rice, Christine E**, M A Animal Diseases Research Inst, Canadian Dept of Agriculture, Hull, Quebec, Canada *Assistant Bacteriologist* (6, 1938)
- Rice, James C**, A M, Ph D University of Mississippi, P O Box 475, University *Professor of Pharmacology* (3, 1941)
- Rich, Arnold** **Rice, M D** Johns Hopkins Hospital, Baltimore, Md *Professor of Pathology, Johns Hopkins University* (4, 1924)
- Richards, Alfred N**, A M, Ph D, Sc D, M D (hon), LL D University of Pennsylvania Medical School, Philadelphia *Professor of Pharmacology and Vice-President in Charge of Medical Affairs, Member, National Academy of Sciences* (1, 1900, 2, 1906, 3, 1909)
- Richards, Oscar W**, M A, Ph D American Optical Co, Scientific Instrument Division, Box A Buffalo 15, N Y *Research Biologist* (1, 1934)
- Richards, Richard Kohn**, M D Abbott Laboratories, North Chicago, Ill *Director, Pharmacologic Research* (1, 1938)
- Richardson, Authur P**, M D Squibb Institute for Medical Research, New Brunswick, N J *Head, Division of Pharmacology* (3, 1939)
- Richardson, Luther R**, Ph D P O Box 102, College Station, Texas (5, 1942)
- Richter, Curt P**, Ph D Phipps Psychiatric Clinic, The Johns Hopkins Hospital, Baltimore, Md *Associate Professor of Psycho-biology, Johns Hopkins University* (1, 1924)
- Richter, Maurice N**, M D 303 E 20th St, New York City *Professor of Pathology, Columbia University, New York Post-Graduate Medical School, Director, Department of Pathology, New York Post-Graduate Medical School and Hospital* (4, 1931)
- Ricketts, Henry T**, M D Dept of Medicine, University of Chicago, Chicago, Ill *Associate Professor of Medicine* (1, 1940)
- Riddle, Oscar**, Ph D Cold Spring Harbor, L I, N Y *Visiting Professor from the U S (in South America), Member of the National Academy of Sciences* (1, 1919)
- Riegel, Byron**, A M, Ph D Department of Chemistry, Northwestern University, Evanston, Ill *Associate Professor* (2, 1912)
- Riegel, Cecilia**, M S, Ph D Room 563, University Hospital, Philadelphia, Pa *Research Associate, Department of Research Surgery, University of Pennsylvania School of Medicine* (2, 1938)
- Ries, Ferd A**, M D 825 E 11st St, Baltimore, Md *Instructor in Neurology, Johns Hopkins University* (1, 1933)
- Rigdon, R H**, M D Univ of Arkansas School of Medicine, Little Rock *Professor of Pathology* (4, 1911)
- Riggs, Lloyd K**, Ph D % Kraft Cheese Co, 500 Peshtigo Court, Chicago, Ill *Director of Research* (2, 1929)
- Rinehart, James F**, M D University of California Medical School, Parnassus and Third Aves, San Francisco *Professor of Pathology* (4, 1933)
- Ring, Gordon C**, M A, Ph D Physiology Dept, Ohio State Univ, Columbus (1, 1933)
- Rioch, David McKenzie**, M D Chestnut Lodge Sanitarium, 500 W Montgomery Ave, Rockville, Md *Director of Research* (1, 1931)
- Rittenberg, David**, Ph D 630 W 168th St, New York City *Assistant Professor, College of Physicians and Surgeons, Columbia University* (2, 1939)
- Ritzman, E G**, A M, Science (hon) University of New Hampshire, Durham *Research Professor* (5, 1933)
- Rivers, T M**, M D, Sc D The Hospital of the Rockefeller Institute for Medical Research, 66th St and York Ave, New York City *Director of the Hospital, Member of the National Academy of Sciences* (4, 1925, 6, 1921)
- Robb, Jane Sands**, Sc D, M D College of Medicine, Syracuse University, 761 Irving Ave, Syracuse, N Y *Associate Professor of Pharmacology* (1, 1924)
- Robbins, Benjamin Howard**, M S, M D Vanderbilt Univ School of Medicine, Nashville, Tenn *Associate Professor of Pharmacology* (3, 1936)
- Robbins, Mary L**, B A, M A, Ph D George Washington Univ School of Medicine, 1335 H Street, N W, Washington 5, D C *Instructor in Bacteriology* (6, 1946)
- Roberts, Edward F**, M D, Ph D Wyeth, Inc 1600 Arch St, Philadelphia 3, Pa *Director of Clinical Investigation* (6, 1932)
- Roberts, Lydia J**, Ph D University of Chicago, Chicago, Ill *Professor and Chairman of Department of Home Economics* (5, 1933)
- Roberts, Sidney**, S B, M S, Ph D Worcester Foundation for Experimental Biology, Shrewsbury, Mass *Research Associate* (1, 1946)

- Robertson, Elizabeth Chant, M D , M A , Ph D University of Toronto, Toronto, Canada *Research Fellow in Paediatrics* (5, 1939)
- Robertson, Oswald H , M D University of Chicago, Chicago, Ill *Professor of Medicine* (4, 1932)
- Robinson, Charles Summers, Ph D Medical School, Vanderbilt University, Nashville, Tenn *Professor of Biochemistry* (2, 1925)
- Robinson, Elliott S , B A , M D , Ph D R F D #4, Laconia, N H *Director, Division of Biologic Laboratories, Mass Dept of Health (Leave of Absence)* (6, 1935)
- Robinson, G Canby, M D , Sc D , LL D Johns Hopkins Hospital, Baltimore, Md *Lecturer in Medicine, Johns Hopkins University* (1, 1912, 3, 1921)
- Robinson, Harry J , Ph D Merck Institute for Therapeutic Research, Rahway, N J *Assistant Director* (3, 1946)
- Robinson, Howard W , M S , Ph D Broad and Ontario Sts , Philadelphia, Pa *Professor of Physiological Chemistry, Temple University School of Medicine* (2, 1929)
- Robinson, Sid, Ph D Indiana University Medical School, Bloomington *Associate Professor of Physiology* (1, 1941)
- Roblin, Richard O , Jr , M A , Ph D 1937 West Main St , Stamford, Conn *Director, Chemotherapy Division, American Cyanamid Co* (2, 1946)
- Robscheit-Robbins, F S , Ph D University of Rochester School of Medicine and Dentistry, Rochester, N Y *Associate in Pathology* (1, 1925, 4, 1930)
- Rodbard, Simon, Ph D Cardiovascular Dept , Michael Reese Hospital, 29th and Ellis Aves , Chicago, Ill (1, 1942)
- Roe, Joseph Hiram, M A , Ph D George Washington University School of Medicine, Washington, D C *Professor of Biochemistry* (2, 1927, 5, 1933)
- Roeder, Kenneth D , M A Tufts College, Medford, Mass *Associate Professor of Biology* (1, 1942)
- Roepke, Martin Henry, Ph D University Farm, St Paul, Minn *Professor, Veterinary Medicine* (3, 1937)
- Rogers, Charles G , A M , Ph D , Sc D Oberlin College, Oberlin, O *Professor of Comparative Physiology* (1, 1911)
- Rogers, Fred T , A M , Ph D , M D Dallas Medical and Surgical Clinic, 4105 Live Oak St , Dallas 1, Texas (1, 1917)
- Rogoff, Julius M , Ph G , M D , Sc D School of Medicine, University of Pittsburgh, Pittsburgh, Pa *Professor of Endocrinology* (1, 1916, 3, 1916)
- Ronzoni, Ethel, M A , Ph D Washington University Medical School, St Louis 4, Mo *Assistant Professor of Biological Chemistry* (2, 1923)
- Root, Howard F , M D 44 Dwight St , Brookline, Mass *Instructor in Medicine, Harvard Medical School* (5, 1933)
- Root, Walter S , Ph D College of Physicians and Surgeons, Columbia University, 630 W 168th St , New York City *Associate Professor of Physiology* (1, 1932)
- Rosahn, Paul D , M D 92 Grand St , New Britain, Conn *Pathologist, New Britain General Hospital, Assistant Clinical Professor of Pathology, Yale University School of Medicine, New Haven* (4, 1934)
- Rose, Anton Richard, M S , Ph D Box 176, Edgewater, N J *Retired* (2, 1916, 5, 1933)
- Rose, William C , Ph D University of Illinois, Urbana *Professor of Biochemistry Member, National Academy of Sciences* (2, 1912, 5, 1933)
- Rosenblueth, Arturo, M D Instituto Nacional de Cardiologia, Calzada de la Piedad 300, Mexico D F , Mexico (1, 1932)
- Rosenfeld, Morris, M D Johns Hopkins School of Medicine, Baltimore, Md *Associate in Pharmacology and Experimental Therapeutics Captain, M C* (3, 1934)
- Rosenow, Edward C , M D , hon LL D and D Sc Research Dept , Longview State Hospital, Cincinnati 16, Ohio (4, 1913, 6, 1915)
- Rosenthal, Otto, M D 4422 Osage Ave , Philadelphia 4, Pa *Associate in Cancer Research, Harrison Dept of Surgical Research and Dept of Physiol Chem, Univ of Pennsylvania* (2, 1946)
- Rosenthal, Sanford M M D National Institute of Health, Bethesda, Md *Senior Pharmacologist, U S Public Health Service* (3 1925)
- Rosenthal, S R , M D , Ph D University of Illinois College of Medicine, Chicago *Assistant Professor of Bacteriology and Public Health in Dept of Pathology and Bacteriology, Director, Tice Laboratory for B C G Vaccination against Tuberculosis, Municipal Tuberculosis Sanatorium* (4, 1941)
- Ross, Joseph F , M D The Robert Dawson Evans Memorial, 65 E Newton St , Boston, Mass *Member of the Department, Physician, Massachusetts Memorial Hospital, Associate Professor of Medicine, Boston University School of Medicine, Welch Fellow of Internal Medicine of the Division of Medical Sciences of the National Research Council* (4, 1941)
- Ross, William F , Ph D Shell Oil Company, 100 Bush St , San Francisco, Calif *Chief Research Chemist* (2, 1940)
- Rostorfer, Howard Hayes, B A , M S , Ph D Department of Physiology , Indiana University ,

- Bloomington, Indiana *Assistant Professor of Physiology* (1, 1946)
- Roth, George B**, M D George Washington Univ 3814 Tea St, N W, Washington 7, D C *Emeritus Professor of Pharmacology* (1, 1914, 3, 1911)
- Roth, Grace M**, M S, Ph D Mayo Clinic, Rochester, Minn *Associate in Clinical Physiology* (1, 1939)
- Rothmund, Paul W** K, Dipl-Ing, Dr-Ing (Munich) Antioch College, Yellow Springs, O *Associate Professor of Biochemistry, and Research Chemist, The C F Kettering Foundation, Antioch College, Associate Professor (Non-resident), Department of Chemistry, Ohio State University* (2, 1940)
- Rous, Peyton**, M D, Sc D Rockefeller Institute for Medical Research, York Ave at 66th St, New York City *Member, Member of the National Academy of Sciences* (4, 1913)
- Routh, Joseph I**, M S, Ph D Chemistry Department, State University of Iowa, Iowa City *Assistant Professor of Biochemistry* (2, 1942)
- Rovenstine, Emery Andrew**, A B, M D 477 First Ave, New York, N Y *Professor of Anesthesia, New York University, Director, Division of Anesthesia, Bellevue Hospital* (3, 1944)
- Rowntree, Jennie I**, M S, Ph D University of Washington, Seattle *Professor of Home Economics* (5, 1933)
- Rowntree, L G**, M D, Sc D, F A C P The Touraine, 1520 Spruce St, Philadelphia, Pa *Director, Philadelphia Institute for Medical Research, Colonel, Medical Reserve, Research Clinician, Philadelphia General Hospital, Chief, Medical Division, Selective Service, National Headquarters, Washington, D C* (1, 1911, 2, 1910, 3, 1908, 4, prior to 1920)
- Rubenstein, Boris B**, Ph D, M D Dept of Metabolic & Endocrine Research, Michael Reese Hospital, East 59th St & Ellis Ave, Chicago, Ill (1, 1934)
- Rubin, Morton A**, Ph D 3732 Gunston Rd, Alexandria, Va *Captain, Signal Corps, Office of the Chief Signal Officer, Military Personnel Division, Washington, D C* (1, 1940)
- Ruch, Theodore C**, M A, Ph D Yale University School of Medicine, New Haven, Conn *Assistant Professor of Physiology* (1, 1933)
- Rusch, Harold Paul**, M D University of Wisconsin Medical School, McArdle Memorial Laboratory, Madison 6 *Professor of Oncology* (4, 1940)
- Russell, Walter C**, Ph D New Jersey Agricultural Experiment Station and Rutgers University, New Brunswick *Biochemist in Nutrition and Professor of Agricultural Biochemistry* (2, 1932, 5, 1933)
- Ryan, Andrew Howard**, M D Chicago Medical School, 710 S Wolcott Ave, Chicago, Ill *Associate Professor of Physiology and Pharmacology* (1, 1912)
- Ryland, David A**, M D Stanford Univ Hospital, San Francisco 15, Calif *Assistant Professor of Medicine, Stanford Univ School of Medicine* (3, 1916)
- Sabin, Florence R**, M D, Sc D 1333 E 10th Ave, Denver 3, Colo *Member Lmeritus, Rockefeller Inst, Member of National Academy of Sciences* (1, 1923)
- Sachs, Ernest**, M D 97 Arundel Pl, St Louis, Mo *Professor Lmeritus of Clinical Neurological Surgery, Washington University Medical School* (1, 1910)
- Sacks, Jacob**, Ph D, M D Endo Products, Inc, 84-10, 101st St, Richmond Hill, N Y *Pharmacologist* (3, 1933)
- Sah, Peter, P T**, M S, Ph D Division of Pharmacology and Experimental Therapeutics, Univ of Calif Medical School, San Francisco, Calif *Lecturer in Pharmacology* (3, 1941)
- Sahyun, Melville**, A M, Ph D Frederick Stearns & Co, 6533 E Jefferson St, Detroit, Mich *Vice President and Director of Research* (2, 1932)
- Salmon, W D**, A M Alabama Polytechnic Institute, Auburn *Animal Nutritionist* (2, 1929, 5, 1933)
- Salter, William T**, B A, M D Yale School of Medicine, 333 Cedar St, New Haven, Conn *Professor of Pharmacology* (1, 1933, 3, 1942, 5, 1934)
- Sammis, Florence E**, M D 136 E 58th St, New York City *Physician, Allergy, O P D, New York Hospital* (6, 1943)
- Sampson, John J**, M D Baxter General Hospital, Spokane, Wash *Major M C* (1, 1932)
- Sampson, Myra M**, A M, Ph D Smith College, Northampton, Mass *Professor of Zoology* (5, 1935)
- Samuels, Leo T**, Ph D University of Utah Medical School, Salt Lake City *Professor and Head of Dept of Biochemistry* (2, 1941, 3, 1937)
- Sandels, Margaret R**, A M, Ph D Florida State College for Women, Tallahassee *Dean of School of Home Economics, Professor of Nutrition* (5, 1933)
- Sandisford, Irene**, Ph D Billings Hospital, University of Chicago, Chicago, Ill *Assistant Professor of Medicine* (2, 1925, 5, 1933)
- Sandow, Alexander**, Ph D Washington Square College, New York University, New York 3, N Y *Assistant Professor of Biology* (1, 1945)
- Sandweiss, David J**, M D 9739 Dexter Ave, Detroit, Mich *Instructor in Clinical Medicine, Wayne University College of Medicine, Physician, Harper Hospital (OPD), Attending Physi-*

- cian Gastroenterology and Gastroscopy, North End Community Fund Clinic* (1, 1944)
 Sanford, Arthur H, A M, M D Clinical Laboratories, Mayo Clinic, Rochester, Minn *Head, Division of Clinical Laboratories* (6, 1920)
 Santos, Francisco O, M S, Ph D University of the Philippines, Los Banos, Laguna *Professor and Head of Department of Agricultural Chemistry, College of Agriculture* (5, 1936)
 Saphir, Otto, M D Michael Reese Hospital, 29th St and Ellis Ave, Chicago 16, Ill *Pathologist, Michael Reese Hospital, Professor of Pathology, University of Illinois Medical School* (4, 1927)
 Sappington, Samuel W, M D, D Sc P O Box 81, Bryn Mawr, Pa *Professor of Pathology, Hahnemann Hospital* (6, 1913)
 Saret, Herbert P, M S, Ph D Tulane Medical School, 1430 Tulane Ave, New Orleans 13, La *Assistant Professor of Biochemistry, Tulane* (2, 1946)
 Saslow, George, Ph D, M D Department of Neuropsychiatry, Washington University Medical School, 640 South Kingshighway, St Louis, Mo *Assistant Professor of Psychiatry Associate Physician to the Student Health Service* (1, 1936)
 Satterfield, G Howard, A M State College of Agriculture and Engineering, University of North Carolina, Raleigh *Professor of Biochemistry* (2, 1944, 5, 1941)
 Saul, Leon Joseph, M A, M D Three Walls Farm, Ridley Creek Rd, Media, Pa (1, 1933)
 Saunders, Felix, Ph D 231 Playa del Sur, La Jolla, Calif (2, 1938)
 Sawyer, Margaret E MacKay, M A, Ph D 142 Lower Albert St, Kingston, Ontario, Canada (1, 1935)
 Sawyer, Wilbur A, M D 3927 Idaho Ave, N W, Washington, D C *Director of Health, United Nations Relief and Rehabilitation Administration* (4, 1930, 6, 1935)
 Saxton, John A, Jr, M D Snodgrass Laboratory of Pathology and Bacteriology, 1426 Carroll St, St Louis, Mo *Assistant Professor of Pathology, Washington University School of Medicine, Medical Director, Pathology, Hospital Division, City of St Louis* (4, 1944)
 Scammon, Richard E, M A, Ph D 172 S E Bedford St, Minneapolis, Minn *Distinguished Service Professor in the Graduate School, University of Minnesota* (1, 1923)
 Schales, Otto, D Sc Ochsner Clinic, Prytanis and Aline Sts, New Orleans, La *Director of Chemical Research, Ochsner Foundation, Director of the Biochemical Laboratory, Ochsner Clinic* (2, 1944)
 Scharles, Frederick H, M D 4228 Alton Place, N W Washington 16, D C (5, 1935)
 Schattenberg, Herbert John, M S, M D Bureau of Laboratories, Medical and Surgical Memorial Hospital, 215 Camden St, San Antonio, Texas *Director* (4, 1940)
 Schenken, John R, M D Univ of Nebraska College of Medicine, Omaha, Neb, *Associate Professor of Pathology and Bacteriology* (4, 1942)
 Scherp, Henry W, M S, Ph D Univ of Rochester School of Medicine and Dentistry, 260 Crittenden Blvd, Rochester 7, N Y *Associate Professor of Bacteriology and Immunology* (6, 1940)
 Schick, Bela, M D 17 E 84th St, New York City *Pediatrician, Mt Sinai Hospital, Sea View Hospital* (6, 1924)
 Schiffrin, Milton J, M S, Ph D *Captain, Altitude Training Section, WWAAB, Walla Walla, Wash* (1, 1943)
 Schlenk, Fritz, Ph D University of Texas, M D Anderson Hospital of Cancer Research, Houston *Biochemist* (2, 1942)
 Schlesinger, M J, Ph D, M D Beth Israel Hospital, 330 Brookline Ave, Boston, Mass *Assistant Professor of Pathology, Harvard Medical School, Director of Pathology, Beth Israel Hospital* (4, 1942, 6, 1921)
 Schlomovitz, Benjamin H, M D 1210 Majestic Bldg, 231 W Wisconsin Ave, Milwaukee, Wis *Director, Clinical and Research Laboratory, Veterans Administration Hospital, Wood, Wisconsin* (1, 1919)
 Schlumberger, Hans G, M D Pathologist, City Hospital, Cleveland, Ohio *Assistant Professor in Pathology, Western Reserve Univ School of Medicine* (4, 1945)
 Schmeisser, Harry C, M D University of Tennessee, Memphis *Professor of Pathology* (4, 1937)
 Schmidt, Carl F, M D Medical School, University of Pennsylvania, Philadelphia *Professor of Pharmacology* (1, 1929, 3, 1924)
 Schmidt, C Robert, Ph D, M D Hertzler Clinic, Halstead, Kan *Resident Surgeon Major (MC) A U S* (1, 1940)
 Schmidt, Gerhard, M D Boston Dispensary, 25 Bennett St, Boston, Mass *Senior Research Fellow, Tufts College Medical School* (2, 1939)
 Schmidt, Leon H, M S, Ph D Christ Hospital, Institute for Medical Research, Cincinnati, O *Director of Research, Assistant Professor of Biological Chemistry, College of Medicine, University of Cincinnati* (2, 1936, 3, 1946)
 Schmitt, Francis Otto, Ph D Dept of Biology and Public Health, Massachusetts Institute of Technology, Cambridge *Professor of Biology* (1 1930)
 Schnedorf, Jerome G, M D, Ph D 801 Simpson St, Evanston, Ill *Captain, M C* (1, 1941)

- Schneider, Edward C , Ph D , Sc D , M P E 25 Gordon Place, Middletown, Conn *University Professor Emeritus, Wesleyan University* (1, 1912, 2, 1912)
- Schneerson, S Stanley, M D Mount Sinai Hospital, 2 East 100th St , New York 29, N Y *Associate Bacteriologist* (6, 1946)
- Schoenbach, Emanuel B , M D Johns Hopkins School of Hygiene, 615 N Wolfe St , Baltimore, Md *Associate Professor of Preventive Medicine* (6, 1941)
- Schoepfle, Gordon M , A M , Ph D Washington University, School of Medicine, St Louis Mo *Assistant Professor of Physiology* (1, 1943)
- Schradieck, Constant E , M D 825 Chalkstone Ave , Providence, R I *Director, Pathological Department, Homeopathic Hospital of Rhode Island* (6, 1921)
- Schreiner, Oswald, M S , Ph D Bureau of Plant Industry, U S Department of Agriculture, Washington 25, D C *Chief, Division of Soil Fertility Investigations* (2, 1908)
- Schroeder, E F , M S , Ph D G D Searle & Co , P O Box 5110, Chicago 80, Ill *Research Biochemist* (2, 1938)
- Schuck, Cecelia, Ph D Purdue University, Lafayette, Ind *Professor of Nutrition, Department of Home Economics* (5, 1941)
- Schultz, Edwin William, M D 743 Cooksey Lane, Stanford University, Calif *Professor of Bacteriology and Experimental Pathology* (4, 1927, 6, 1928)
- Schultz, Mark P , A M , M D National Institute of Health, Bethesda, Md *Surgeon, U S Public Health Service* (6, 1933)
- Schultz, W H , Ph D 3102 18th St , N W , Washington, D C *Professor of Pharmacology, Emeritus, University of Maryland* (1, 1907, 3, 1909)
- Schultz, Max O , Ph D Division of Agricultural Biochemistry, Univ of Minnesota, St Paul 8, Minn *Professor* (2, 1938)
- Schwartz, Erich W , M D 1225 Talbert St , S E , Washington, D C (3, 1920)
- Schweizer, Malvina, Ph D Washington Square College of Arts and Sciences, New York University, New York, N Y *Instructor in Biology* (1, 1944)
- Scott, Charles Covert, Ph D , M D The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis 6, Ind *Pharmacologist* (3, 1945)
- Scott, David Alymer, M A , Ph D Connaught Laboratories, University of Toronto, Toronto 5, Ontario, Canada *Research Member* (2, 1935)
- Scott, Ernest L , Ph D 64 South St , Bogota, N J *Associate Professor of Physiology, Emeritus, Columbia University* (1, 1914, 2, 1915)
- Scott, Frederick Hughes, Ph D , Sc D , M B University of Minnesota, Minneapolis *Professor of Physiology, Emeritus* (1, 1908, 2, 1909)
- Scott, John C , Ph D Hahnemann Medical College, Philadelphia, Pa *Professor of Physiology and Head of the Department* (1, 1936)
- Scott, R W , A M , M D City Hospital, Cleveland, O *Professor of Clinical Medicine, Western Reserve University, Physician-in-chief, Cleveland City Hospital* (1, 1917, 3, 1917)
- Scott, V Brown, Ph D , M D Inlow Clinic, Shelbyville, Ind *Internist, Division of Medicine* (1, 1911)
- Scott, W J Merle, M D University of Rochester Medical School, Rochester, N Y *Associate Professor of Surgery* (4, 1925)
- Scott, W W , M D Brady Urological Inst , The Johns Hopkins Hospital, Baltimore 5, Md (1, 1913)
- Scudi, John Vincent, Ph D Dept of Pharmacology, College of Physicians and Surgeons, Columbia Univ , 630 West 168th St , New York 32, N Y (2, 1942, 5, 1945)
- Seager, Lloyd D , M S , M D Woman's Medical College of Pennsylvania, East Falls, Philadelphia *Professor of Pharmacology and Toxicology* (3, 1939)
- Sealock, Robert R , Ph D Iowa State College, Ames *Associate Professor of Chemistry* (2, 1940, 5, 1941)
- Seastone, C V , Jr , M D University of Wisconsin Medical School, Madison *Professor of Medical Bacteriology* (6, 1939)
- Sebrell, W H , Jr , M D National Institute of Health, Bethesda, Md *Chief, Division of Physiology* (2, 1938, 5, 1937)
- Seecof, David P , M D 1970 Daly Ave , Bronx, New York City (4, 1927)
- Seegal, David, M D Welfare Island, New York City *Director, Research and Clinical Service, First Division, Goldwater Memorial Hospital; Associate Professor of Medicine, Columbia University* (6, 1930)
- Seegers, Walter H , Ph D Wayne University College of Medicine, Detroit 26, Mich *Associate Professor* (2, 1941)
- Seevers, Maurice Harrison, Ph D , M D University of Michigan School of Medicine, Ann Arbor *Professor of Pharmacology and Chairman of the Department* (1, 1933, 3, 1930)
- Segaloff, Albert, M D Alton Ochsner Medical Foundation, 3503 Prytania St , New Orleans, La *Director of Endocrine Research* (4, 1946)
- Seibert, Florence B , Ph D , Sc D , LL D Henry Phipps Institute, University of Pennsylvania, 7th and Lombard Sts , Philadelphia *Associate Professor of Biochemistry* (2, 1925)
- Seidell, Atherton, M S , Ph D 2301 Connecticut Ave , Washington, D C *Special Expert, National Institute of Health* (2, 1924)
- Seifter, Joseph, M D Wyeth Institute of Applied

- Biochemistry, Philadelphia, Pa *Chief Pharmacologist* (3, 1940)
- Seifter, Sam, M S , Ph D 350 Henry St , Brooklyn 2, N Y *Assistant Professor of Biochemistry, Long Island College of Medicine* (2, 1946)
- Selkurt, Ewald E , Ph D School of Medicine, Western Reserve University, Cleveland 6, O *Senior Instructor in Physiology* (1, 1945)
- Selle, Wilber Arthur, Ph D Medical School, University of Texas, Galveston *Professor of Physiology* (1, 1938)
- Selye, Hans, M D , Ph D , D Sc , F R S (c) Inst of Experimental Medicine and Surgery Univ of Montreal, Montreal, Canada *Professor and Director* (1, 1934)
- Sendroy, Julius, Jr, M A , Ph D Mercy Hospital, 2537 Prairie Ave , Chicago, Ill *Professor of Chemistry and Chairman of the Department of Experimental Medicine, Loyola University School of Medicine* (2, 1928)
- Serag, M G , Ph D Department of Bacteriology, University of Pennsylvania School of Medicine, Philadelphia *Assistant Professor of Biochemistry in Bacteriology* (6, 1941)
- Serringhaus, Elmer L , M A , M D Hoffman-La Roche, Inc , Nutley 10, N J *Director of Clinical Research, Consulting in Endocrinology, New York Univ Med School* (2, 1923, 5 1939)
- Shaffer, Morris F , D Phil Department of Pathology and Bacteriology, School of Medicine, Tulane University of Louisiana, New Orleans *Associate Professor* (4, 1939, 6, 1937)
- Shaffer, Philip A , Ph D Washington University Medical School, St Louis 4, Mo *Distinguished Service Professor of Biological Chemistry, Member National Academy of Sciences* (1, 1906, 2, 1906, 5, 1935)
- Shanes, Abraham M , M S , Ph D 1045 Anderson Ave , Bronx 52, N Y *Assistant Professor of Physiology* (1, 1946)
- Shannon, James A , Ph D , M D Squibb Institute for Medical Research, New Brunswick, N J *Director, Squibb Institute for Medical Research* (1, 1933, 3, 1945)
- Shapiro, Herbert, Ph D Box 63, Edgewood, Md (1, 1937)
- Sharpless, George R , M S , Sc D RD #2, Box 160 New York, N Y *Associate in Nutrition Research* (5, 1942)
- Shaw, Myrtle, M S , Ph D 11 S Lake Ave , Albany, N Y *Senior Bacteriologist, Division of Laboratories and Research, New York State Department of Health* (6, 1937)
- Shay, Harry, M D Samuel S Fels Fund, Medical Tower, Philadelphia, Penna *Director, Medical Research Laboratory* (1, 1944)
- Shear, Murray, J , Ph D National Cancer Institute, Bethesda, Md *Principal Biochemist* (2, 1930)
- Sheard, Charles, A M , Ph D Mayo Foundation, Rochester, Minn *Chief of the Division of Physics and Biophysical Research and Professor of Physiological Optics and Biophysics, University of Minnesota* (1, 1925)
- Sheehan, Donal, M D , D Sc New York University College of Medicine, First Ave , New York City *Professor of Anatomy and Director of Anatomical Laboratories* (1, 1938)
- Shelley, Walter Brown, Ph D 1214 Perkins St , Chester, Pa *Research Staff* (1, 1946)
- Shemin, David, A M , Ph D Columbia University, College of Physicians and Surgeons, 630 W 168th St , New York City *Assistant Professor of Biochemistry* (2, 1944)
- Sheppard, Fay, M S University of Oklahoma Medical School, Oklahoma City *Instructor in Biochemistry* (2, 1936)
- Sherman, Henry C , A M , Ph D , Sc D Columbia University, New York City *Mitchell Professor Emeritus of Chemistry, Member, National Academy of Sciences* (1, 1923, 2, 1906, 5, 1933)
- Sherwin, Carl Paxson, Sc D , M D , Dr P H , LL D 6 Carstensen Rd , Scarsdale, N Y *Director of Metabolic Service, St Vincent's Hospital, Associate Physician, French Hospital* (1, 1919, 2, 1917)
- Sherwood, Noble P , Ph D , M D 1801 Indiana St , Lawrence, Kan *Professor of Bacteriology, University of Kansas* (6, 1928)
- Sherwood, Thomas Cecil, M A , Ph D , 1824 Robert St , New Orleans, La (1, 1938)
- Shettles, Landrum B , Ph D , M D 2827 Guilford Ave , Baltimore 18, Md *Medical Officer, U S Army* (1, 1946)
- Shideman, Frederick E , B A , Ph D Dept of Pharmacology, University of Michigan, Ann Arbor *Instructor of Pharmacology* (3, 1944)
- Shumkin, Michael Boris, M D U S Public Health Service, National Cancer Institute, Bethesda, Md *Surgeon* (4, 1940)
- Shipley, Reginald A , M D Western Reserve University School of Medicine, Cleveland 6, O *Assistant Professor of Medicine* (1, 1945)
- Shipley, Robert E , M D Lilly Laboratory for Clinical Research, Indianapolis City Hospital, Indianapolis, Ind (1, 1945)
- Shlaer, Simon, M A , Ph D Columbia University, New York City *Research Associate in Biophysics* (1, 1938)
- Shock, Nathan W Ph D Unit on Gerontology, U S Public Health Service, Baltimore City

- Hospitals, Baltimore, Md *Senior Psychophysiological, U S Public Health Service, National Institute of Health, Bethesda, Md* (1, 1942)
- Shoemaker, Harold A**, M S, Ph D University of Oklahoma School of Medicine, 801 E 13th St, Oklahoma City *Assistant Dean, Professor of Pharmacology* (3, 1941)
- Shope, Richard E**, M D Department of Animal and Plant Pathology, The Rockefeller Institute, Princeton, N J *Member* (4, 1934)
- Shorr, Ephraim, B A**, M D The New York Hospital, 525 East 68th St, New York City *Associate Professor of Medicine, Cornell University Medical College, Assistant Attending Physician, The New York Hospital* (1, 1931, 3, 1942)
- Shwartzman, Gregory**, M D 230 E 50th St, New York City *Head of Department of Bacteriology, Mount Sinai Hospital, Clinical Professor of Bacteriology, Columbia University* (4, 1929, 6, 1930)
- Sichel, F J M**, Sc M, Ph D College of Medicine, University of Vermont, Burlington *Associate Professor of Physiology* (1, 1939)
- Sickles, Grace M**, B A 2201 Twelfth St, Troy, N Y *Associate Bacteriologist, Division of Laboratories and Research, New York State Department of Health* (6, 1932)
- Sickles, Gretchen R**, A B Division of Laboratories and Research, New York State Department of Health, Albany, N Y *Assistant Bacteriologist* (6, 1937)
- Siebenmann, Charles O**, Ch E, D Eng Connaught Medical Research Laboratories, Univ of Toronto, Toronto 5, Ontario, Canada *Research Associate* (3, 1946)
- Siebert, Walter J**, M D DePaul Hospital, St Louis 13, Mo *Director of Laboratories and Pathologist of DePaul and Lutheran Hospitals, St Louis, and of St Joseph Hospital, Alton, Ill, St Elizabeth's Hospital, Belleville, Ill, St Francis Hospital, Washington, Mo* (4, 1932)
- Silberberg, Martin**, M D Snodgrass Laboratory of Pathology, City Hospital, 1430 Carrol St, St Louis 4, Mo *Instructor in Pathology, Washington University, School of Medicine* (4, 1944)
- Silberberg, Ruth**, M D Jewish Hospital, St Louis, Mo *Instructor in Pathology, Washington University Medical School* (4, 1944)
- Silvette, Herbert**, M S, Ph D University of Virginia Medical School, University *Acting Head of Pharmacology* (1, 1933, 3, 1940)
- Simon, Frank A**, M D 332 West Broadway, Louisville, Ky (6, 1934)
- Simonds, James P**, Ph D, M D Northwestern University Medical School, 234 E Pearson St, Chicago 2, Ill *Lumetus Professor of Pathology* (4, prior to 1920)
- Simonson, Ernst**, M D c/o Laboratory of Physiological Hygiene, Stadium South Tower, University of Minnesota, Minneapolis 11 *Associate Professor of Physiological Hygiene and of Physiology* (1, 1911)
- Simpson, Miriam E**, M A, Ph D, M D Div of Anatomy, Univ of Calif, Berkeley, Calif *Professor of Anatomy* (1, 1916)
- Sinclair, Robert Gordon**, Ph D, F R S C, Queen's University, Kingston, Ont, Canada *Professor of Biochemistry* (2, 1931)
- Sizer, Irwin W.**, Ph D Massachusetts Institute of Technology, Cambridge *Associate Professor of Physiology* (1, 1914)
- Skinner, John Taylor**, M S, Ph D c/o The Grapette Co, Camden, Arkansas *Chief Chemist* (2, 1946)
- Slaughter, Donald**, M D Univ of South Dakota, Vermillion, S D *Dean* (3, 1938)
- Slonaker, James R**, Ph D 334 Kingsley Ave, Palo Alto, Calif *Professor of Physiology, Leland Stanford Junior University* (1, 1917)
- Smadel, Joseph Edwin**, M D Hospital of The Rockefeller Institute for Medical Research, 66th St and York Ave, New York, N Y *Associate Member, Asst Physician, Rockefeller Hospital* (4, 1940, 6, 1937)
- Small, James C**, M D 133 S 36th St, Philadelphia, Pa *Instructor in Medicine, Graduate School of Medicine, University of Pennsylvania* (4, 1927)
- Smetana, Hans F**, M D Army Institute of Pathology, 7th St, and Independence Ave, Washington 25, D C (4, 1934)
- Smith, Arthur H**, M S, Ph D Wayne University College of Medicine, Detroit 26, Mich *Professor of Physiological Chemistry* (1, 1923; 2, 1921, 5, 1933)
- Smith, Austin Edward**, M D, C M, M Sc (Med) - American Medical Association, 535 N Dearborn St, Chicago, Ill *Acting Secretary of the Council on Pharmacy and Chemistry, American Medical Association, Research Associate (Instructor) Dept of Pharmacology, University of Chicago* (3, 1942)
- Smith, Clarence A**, M S, Ph D Standard Brands, Inc, 595 Madison Ave, New York City *Technical Director, Special Products Department* (1, 1921)
- Smith, David T** Duke Hospital, Durham, N C (5, 1943)
- Smith, Dietrich Conrad**, A M, Ph D University of Maryland School of Medicine, Lombard and Greene Sts, Baltimore *Associate Professor of Physiology* (1, 1937)

- Smith, Elinor Van Dorn, Ph D 5 Middle St, Hadley, Mass Associate Professor of Bacteriology, *Smith College* (6, 1940)
- Smith, Elizabeth R B, Ph D c/o Dr Paul K Smith, 1335 H St, N W, Washington 5, D C (2, 1938)
- Smith, Emil L, Ph D School of Medicine, Univ of Utah, Salt Lake City 1, Utah Associate Professor, *Biochemistry and Physiology* (2, 1946)
- Smith, Erma A, M A, Ph D, M D Infirmary, East Campus, Duke University, Durham, N C (1, 1928)
- Smith, Fred M, M D State University of Iowa, Iowa City Professor of the Theory and Practice of Medicine and Head of the Department (1, 1925)
- Smith, George H, M A, Ph D, M A (hon), Sc D School of Medicine, Yale University, New Haven, Conn Professor of Immunology and Assistant Dean, Chairman, Department of Bacteriology, *Yale University* (6, 1918)
- Smith, H P, M S, M D Columbia Univ, Coll of Physicians and Surgeons, 630 West 168th St, New York 32, N Y *Delafield Professor of Pathology* (1, 1937, 4, 1925)
- Smith, Homer W, M S (hon), Sc D 477 First Ave, New York City Professor of Physiology, *New York University College of Medicine*, Member, *National Academy of Sciences* (1, 1923, 2, 1930)
- Smith, Lawrence Weld, M D 745 Fifth Ave, New York 22, N Y (4, 1927)
- Smith, Lee Irvin, A M, Ph D School of Chemistry, University of Minnesota, Minneapolis Professor and Chief, Division of Organic Chemistry (2, 1942)
- Smith, Margaret Cammack, A M, Ph D El Encanto Estates, Tucson, Arizona (2, 1935, 5, 1933)
- Smith, Maurice I, M D National Institute of Health, Bethesda, Md Principal Pharmacologist, *U S Public Health Service* (1, 1920, 3, 1916)
- Smith, Paul K, Ph D George Washington Univ School of Medicine, 1335 H St, N W, Washington 5, D C Professor of Pharmacology (2 1937, 3, 1937)
- Smith, Paul W, M S, Ph D School of Medicine, University of Oklahoma, 801 E 13th St, Oklahoma City Assistant Professor of Pharmacology (1, 1933)
- Smith, Philip Edward, M S, Ph D 630 W 168th St, New York City Professor of Anatomy, *Columbia University*, Member of the *National Academy of Sciences* (1, 1923)
- Smith, Ralph G, M D, Ph D Tulane University, Station 20, New Orleans, La Professor of Pharmacology (3, 1929)
- Smith, R Blackwell, Jr, B S, M S, Ph D Medical College of Virginia, Richmond 19, Va Lecturer in Pharmacology (3, 1944)
- Smith, Sedgwick E, Ph D Dept Animal Husbandry, Cornell University, Ithaca, N Y *Animal Physiologist* (5, 1945)
- Smith, Susan Gower, M A Duke University, Durham, N C Associate, *Department of Medicine and Nutrition, School of Medicine* (5, 1939)
- Smith, Sybil L, A M Principal Experiment Station Administrator, Office of Experiment Stations, U S D A, Washington, D C (5, 1940)
- Smith, Wilbur Kenneth, M D University of Rochester School of Medicine and Dentistry, 260 Crittenden Blvd, Rochester, N Y Associate Professor of Anatomy (1, 1939)
- Smith, Willie W, M A, Ph D 4710 Edgmoor Lane, Bethesda, Md Associate Physiologist, *National Institute of Health* (1, 1941)
- Smithburn, Kenneth C, M D Yellow Fever Research Institute, P O Box 49, Entebbe, Uganda, British East Africa Staff Member, *International Health Division of The Rockefeller Foundation* (6, 1937)
- Smolens, Joseph, B S Wyeth Research Inst, 900 N Broad St, Philadelphia, Pa Head, Dept of Immunology (6, 1943)
- Smythe, C V, M S, Ph D 5000 Richmond St Philadelphia, Pa Head of *Biochemistry, Rohm & Haas Company* (2, 1934)
- Snell, Albert M, M D Mayo Clinic, Rochester, Minn Head of Section on Medicine at Mayo Clinic, Professor in Medicine, *Mayo Foundation Graduate School, University of Minnesota* (4, 1930)
- Snell, Esmond E, M A, Ph D University of Wisconsin, Madison 6 Associate Professor of Biochemistry (2, 1942, 5, 1946)
- Snyder, Charles D, M S, Ph D Baltimore 10, Md Professor Emeritus of Experimental Physiology, *Johns Hopkins Univ* (1, 1907)
- Snyder, Franklin Faust, M D Boston Lying-In Hospital, Boston, Mass (1, 1936)
- Sobel, Albert E, Ch E, M A, Ph D Jewish Hospital of Brooklyn, Prospect Place and Classon Ave, Brooklyn, N Y Director of Chemical Laboratories, Lecturer in Biochemistry, Graduate Division, Brooklyn College, Lecturer in "Blood Chemistry", Hunter College, Lecturer in Chemistry, Polytechnic Institute of Brooklyn (2, 1939)
- Sobotka, Harry H, Ph D Mount Sinai Hospital, Fifth Ave and 100th St, New York City Head, Department of Chemistry (2, 1932, 5, 1933)
- Solandt, Donald Young, M A, M D, Ph D Uni-

- versity of Toronto, Toronto, Ont, Canada
Associate Professor of Physiology, Head of the
Department of Physiological Hygiene (1, 1937)
- Soley, Mayo H, M D University of California
Medical School, The Medical Center, San Fran-
cisco Associate Professor of Medicine and
Assistant Dean (1, 1943)
- Sollmann, Torald, M D Sc D, LL D School of
Medicine, Western Reserve University, 2109
Adelbert Rd, Cleveland, O Dean and Professor
of Pharmacology and Materia Medica, Emeritus
(1, 1902, 2, 1906, 3, 1908)
- Solotorovsky, Morris, Major, M S 203 W 5th St,
Plainfield, N J (6, 1946)
- Somogyi, Michael, Ph D 216 S Kingshighway,
St Louis, Mo Biochemist, Jewish Hospital
of St Louis (2, 1927)
- Soskin, Samuel, M D, M A, Ph D Michael
Reese Hospital, Chicago, Ill Director of Meta-
bolic and Endocrine Research, Professoral Lec-
turer in Physiology, University of Chicago
(1, 1930, 5, 1933)
- Soule, Malcolm H, Sc D, LL D University of
Michigan, Ann Arbor Professor of Bacteriol-
ogy, and Chairman of the Department of Bacteri-
ology (4, 1927, 6, 1925)
- Spain, Will C, M D, F A C P 116 E 53rd St,
New York City Clinical Professor of Medicine,
Post-Graduate Medical School, Columbia Uni-
versity (6, 1923)
- Spealman, C R, M A, Ph D Dept of Physiology
Univ of Pennsylvania School of Medicine, Phila-
delphia, Pa (1, 1940)
- Specht, Heinz, Ph D National Institute of
Health, Rockville Pike, Bethesda, Md Asso-
ciate Research Physiologist (1, 1941)
- Sperry, Roger W, Ph D Dept of Anatomy, Uni-
versity of Chicago, Chicago 37, Ill (1, 1945)
- Sperry, Warren M, M S, Ph D 722 W 168th St,
New York City Principal Research Biochemist,
New York State Psychiatric Institute and Hos-
pital, Associate Professor of Biological Chemis-
try, College of Physicians and Surgeons, Columbia
University (2, 1929, 5, 1933)
- Spiegel, Ernest A, M D Temple University
School of Medicine, Broad and Ontario Sts,
Philadelphia, Pa Professor of Experimental
Neurology (1, 1936)
- Spiegel-Adolf, Mona, M D Temple University
School of Medicine, Broad St at Ontario Ave,
Philadelphia, Pa Professor and Head of De-
partment of Colloid Chemistry (2, 1933)
- Spiegelman, Sol, Ph D Washington Univ School
of Medicine, St Louis, Mo Instructor in Bacteri-
ology (1, 1946)
- Spies, Tom D, M D Feb-Nov Hillman Hos-
pital, Birmingham, Ala Nov-Feb General
Hospital, Cincinnati, O Associate Professor
of Medicine, Univ of Cincinnati College of
Medicine Visiting Professor of Medical Re-
search, Univ of Alabama School of Medicine
Professor of Medical Research, Univ of Texas
School of Medicine Director, Nutrition Clinic,
Hillman Hospital, Birmingham, Ala (3, 1941,
4, 1910, 5, 1938)
- Spink, Wesley W, M D University of Minnesota
Hospital, Minneapolis Professor of Medicine,
University of Minnesota Medical School (3,
1910, 4, 1910, 6, 1910)
- Spohn, Adelaide, M S, Ph D Elizabeth McCor-
mick Memorial Fund, 848 N Dearborn St,
Chicago, Ill (5, 1933)
- Spoor, Herbert J, Ph D 152nd St and 89th
Ave, Jamaica, N Y Mary Immaculate Hos-
pital, Internship (1, 1915)
- Sprout, Edith E, M D Dept of Pathology, Amer-
ican Univ of Beirut, Beirut, Lebanon Professor
of Pathology (1, 1911)
- Sprunt, Douglas H, M D, M S Univ of Tennes-
see, Memphis Professor of Pathology (4, 1934,
6, 1936)
- Stadie, William C, M D 821 Maloney Clinic,
36th and Spruce Sts, Philadelphia, Pa Pro-
fessor of Research Medicine, University of Penn-
sylvania (2, 1922)
- Stainsby, Wendell J, M D, C M Geisinger
Memorial Hospital, Danville, Pa Chief Physi-
cian (6, 1930)
- Stanley, Wendell M, M S, Ph D, Sc D Rocke-
feller Institute for Medical Research, Princeton,
N J Member, Member, National Academy of
Sciences (2, 1936)
- Stannard, James Newell, Ph D Industrial Hy-
giene Research Lab, National Institute of
Health, U S Public Health Service, Bethesda
14, Md Senior Pharmacologist (1, 1938)
- Stare, Frederick J, Ph D, M D 695 Huntingdon
Ave, Boston 15, Mass Associate Professor of
Nutrition, Harvard Medical School and Harvard
School of Public Health (2, 1937, 5, 1942)
- Starr, Isaac, B S, M D 817 Maloney Clinic, Hos-
pital of the University of Pennsylvania, Phila-
delphia Dean of the School of Medicine, Professor
of Therapeutic Research (1, 1929, 3, 1942)
- Stavraky, George W, M D, C M, M Sc Medi-
cal School, University of Western Ontario,
London, Ont, Canada Associate Professor of
Physiology (1, 1937, 3, 1944)
- Stead, Eugene A, Jr, M D Emory University
Medical School, Atlanta, Ga Professor of
Medicine (1, 1945)
- Stearns, Genevieve, Ph D College of Medicine,
State University of Iowa, Iowa City Research
Professor of Pediatrics (2, 1932, 5, 1937)
- Steel, Matthew, Ph D Long Island College of
Medicine, 350 Henry St, Brooklyn, N Y Pro-
fessor of Biological Chemistry (2, 1909)

- Steele, J Murray, M D Welfare Hospital, Welfare Island, New York City Associate Professor of Medicine, New York University, Director 3rd (New York University) Medical Division of Welfare Hospital (1, 1936)
- Steenbock, Harry, M S, Ph D, Sc D University of Wisconsin, Madison Professor of Biochemistry (2, 1912, 5, 1933)
- Steggerda, F R, M A, Ph D 416 Natural History Building, University of Illinois, Urbana Assistant Professor of Physiology (1, 1934)
- Stehle, Raymond Louis, A M, Ph D Faculty of Medicine, McGill University, Montreal, Canada Professor of Pharmacology (2, 1920, 3, 1922)
- Steigmann, Frederick, M S, M D 348 S Hamlin Ave, Chicago, Ill Associate in Medicine, College of Medicine, University of Illinois, Associate Attending Physician, Cook County Hospital (3, 1942)
- Steiman, S E, M A, Ph D M D 1874 Commonwealth Ave, Brighton Mass Assistant Physician, Metropolitan State Hospital, Waltham, Mass (1, 1939)
- Stein, William Howard, Ph D The Rockefeller Institute for Medical Research, 66th and York Ave, New York 21, N Y Associate in Chemistry (2, 1946)
- Steinbach, H Burr, M A, Ph D Washington University, St Louis, Mo Associate Professor of Zoology (1, 1934)
- Steinberg, Bernhard, M D Toledo Hospital Institute of Medical Research, Toledo, O Director of the Toledo Hospital Institute of Medical Research, Director of Clinical and Morbid Pathological Laboratories, The Toledo Hospital, Surgeon, U S P H (inactive) (4, 1928)
- Steiner, Paul E, M D The University of Chicago, Chicago, Ill Associate Professor of Pathology (4, 1939)
- Steinhardt, Jacinto, A M, Ph D 1548 East-West Highway, Silver Spring, Md Director of Research, Project 8897, Mass Institute of Technology (2, 1939)
- Steinhaus, Arthur H, M S, Ph D, M P E 5315 Drexel Ave, Chicago, Ill Professor of Physiology, George Williams College, Hyde Park (1, 1928)
- Stekol, Jakob A, M A, D Sc Amino Products Division, Rossford, O Principal Research Chemist (2, 1936)
- Stern, Kurt G, Ph D 85 Livingston St, Brooklyn, N Y Lecturer in Chemistry, Polytechnic Institute (2, 1938)
- Stetten, DeWitt, Jr, M D, Ph D 630 W 168th St, New York City Assistant Professor of Biochemistry, College of Physicians and Surgeons, Columbia University (2, 1944)
- Stevens, S Smith, Ph D Emerson Hall, Harvard University, Cambridge, Mass Assistant Professor of Psychology (1, 1937)
- Stewart, Fred W, M D Memorial Hospital, 444 E 68th St, New York City Pathologist, Associate Professor of Surgical Pathology, Cornell Medical School, Pathologist, New York State Department of Public Health, Division of Laboratories and Research (4, 1928)
- Stewart, Harold L, M D The National Cancer Institute, Bethesda, Md Senior Pathologist (4, 1936)
- Stewart, Winifred Bayard, M D, M A 2028 Delancey St, Philadelphia, Pa Professor of Neurology, Woman's Medical College of Pennsylvania (1, 1941)
- Stickney, J Clifford, M S, Ph D West Virginia University School of Medicine, Morgantown Assistant Professor of Physiology (1, 1944)
- Stiebeling, Hazel K, M A, Ph D United States Department of Agriculture, Washington, D C Chief, Bureau of Human Nutrition and Home Economics (5, 1933)
- Stier, Theodore J B, Ph D Indiana University Medical School, Bloomington Associate Professor of Physiology (1, 1938)
- Still, Eugene U, Ph D % Strong Cobb & Co, 2654 Lisbon Rd, Cleveland, O (1, 1929)
- Stillman, Ernest G, M D 45 E 75th St, New York City (6, 1930)
- Stockton, Andrew Benton, M D Barracks Dispensary, U S Naval Supply Depot, Oakland, Calif Assistant Clinical Professor of Medicine, Stanford Medical School, Commander, (M C) U S N R (3, 1931)
- Stokstad, E L Robert, Ph D Lederle Laboratories, Pearl River, N Y Research Chemist (5, 1942)
- Stoland, O O, M S, Ph D 1845 Learned Ave, Lawrence, Kan Professor of Physiology and Pharmacology, University of Kansas (1, 1913)
- Stone, William E, Ph D Department of Surgery, Wayne University College of Medicine, Detroit 26, Mich Research Associate with rank of Instructor (1, 1945)
- Stormont, Robert T, Ph D, M D Medical Division, Food and Drug Administration, Washington, D C (3, 1941)
- Stotz, Elmer H, Ph D New York State Agricultural Experiment Station, Cornell University Geneva, N Y Professor of Agricultural and Biological Chemistry, Cornell University (2, 1939)
- Stoughton, Roger W, M S, Ph D Mallinckrodt Chemical Works, 3600 N Second St, St Louis, Mo Research Chemist (3, 1939)
- Strong, Frank M, M A, Ph D Department of Biochemistry, University of Wisconsin, Madison Associate Professor of Biochemistry (2, 1941)

- Struck, Harold Carl**, Ph D Dept of Pharmacology, Temple Univ School of Medicine, Broad and Ontario Sts, Philadelphia, Pa (1, 1910)
- Stuart, Charles A**, M Sc, Ph D 372 Lloyd Ave, Providence, R I *Associate Professor of Biology, Brown University* (6, 1935)
- Sturgis, Cyrus Cressey**, M D Simpson Memorial Institute, Ann Arbor, Mich *Director, Thomas Henry Simpson Memorial Institute for Medical Research, Chairman, Department of Medicine, University Hospital, and Professor of Medicine, University of Michigan* (4, 1927)
- Stutzman, Jake W**, Ph D Dept of Physiology, Univ of Wisconsin, Madison 6, Wis *Assistant Professor of Physiology* (1, 1946)
- SubbaRow, Y**, Ph D Lederle Laboratories, Pearl River, N Y (2, 1939)
- Sugg, John Y**, Ph D Cornell University Medical College, 1300 York Ave, New York City *Associate Professor of Bacteriology and Immunology* (6, 1938)
- Sulkin, S Edward**, Ph D Southwestern Medical Foundation, Dallas, Texas *Professor of Bacteriology and Immunology* (6, 1944)
- Sullivan, Michael Xavier**, Ph D Chemo-Medical Research Institute, Georgetown University, 37th & O Sts, N W, Washington, D C *Director and Research Professor of Chemistry* (2, 1909)
- Sulzberger, Marion B**, M D 962 Park Ave, New York 28, N Y *Associate Clinical Professor of Dermatology and Syphilology, N Y Post-Graduate Medical School of Columbia Univ, Assoc Director, Skin and Cancer Unit of N Y Post-Graduate Hospital* (6, 1936)
- Summerson, William H**, M A, Ph D Cornell University Medical College, 1300 York Ave, New York City *Associate Professor of Biochemistry* (2, 1942)
- Sumner, James Batcheller**, A M, Ph D Dairy Building, Ithaca, N Y *Professor of Biochemistry, Cornell University* (2, 1919)
- Sumwalt, Margaret**, M S, Ph D Medical School, University of Pennsylvania, Philadelphia (1, 1934)
- Sunderman, F William**, M D, Ph D University of Pennsylvania, Philadelphia *Assistant Professor of Research Medicine* (2, 1931)
- Sundstroem, Edward S**, M D University of California, Berkeley *Professor of Biochemistry* (2, 1919)
- Sure, Barnett**, M S, Ph D University of Arkansas, Fayetteville *Head of Department and Professor of Agricultural Chemistry* (2, 1923, 5, 1933)
- Sutherland, George F**, C M, M D, M Sc Crile General Hospital, Cleveland, O *Major, M C* (1, 1939)
- Sutton, T Scott**, M Sc, Ph D Ohio State University, Columbus *Professor, Ohio State University, Associate, Ohio Agricultural Experiment Station, Director, Institute of Nutrition and Food Technology* (5, 1936)
- Svirbely, Joseph L**, Ph D Industrial Hygiene Research Laboratory, National Institute of Health, Bethesda 11, Md *Pharmacologist* (3, 1915)
- Swain, Robert E**, M S, Ph D, LL D 634 Mirada Ave, Stanford University, Calif *Professor Emeritus of Chemistry* (2, 1909)
- Swann, Howard G**, M S, Ph D Dept of Pharmacology, University of Texas Medical School, Galveston *Assistant Professor of Physiology Captain, Aero Medical Laboratory, Wright Field, Dayton, O* (1, 1910)
- Swanson, Pearl P**, M S, Ph D Iowa State College, Ames *Professor of Foods and Nutrition, Dept of Foods and Nutrition* (5, 1933)
- Swanson, William W**, M S, M D 2376 E 71st St, Chicago, Ill *Assistant Professor of Pediatrics, Northwestern University* (2, 1938)
- Sweeney, H Morrow**, M S, Ph D School of Medical Sciences, University of South Dakota, Vermillion *Professor of Physiology and Pharmacology and Head of the Department* (1, 1939)
- Sweet, J E**, A M, M D, Sc D Unadilla, N Y *Emeritus Professor of Surgical Research, Cornell Medical College* (1, 1913)
- Swift, Homer**, M D, D Sc 888 Park Ave, New York City *Member, Rockefeller Institute for Medical Research, Physician to The Hospital of The Rockefeller Institute for Medical Research* (6, 1920)
- Swift, Raymond W**, M S, Ph D Pennsylvania State College, State College *Professor, Department of Animal Nutrition* (5, 1934)
- Swingle, Wilbur Willis**, Ph D Princeton University, Princeton, N J *Professor of Biology* (1, 1924)
- Sydenstricker, V P** University of Georgia School of Medicine, Augusta *Professor of Medicine* (5, 1944)
- Sykes, Joseph F**, M S A, Ph D U S Dept of Agriculture, Bureau of Dairy Industry, Beltsville, Md *Physiologist* (1, 1942)
- Syverton, Jerome T**, M D The University of Rochester School of Medicine and Dentistry and Strong Memorial Hospital, Rochester, N Y *Associate Professor of Bacteriology* (4, 1940)
- Szego, Clara M**, M S, Ph D Worcester Foundation for Experimental Biology, Shrewsbury, Mass *Research Associate* (1, 1946)
- Tainter, M L**, M A, M D Sterling-Winthrop Research Institute, 33 Riverside Ave, Rennselaer, N Y *Director of Research* (1, 1929, 3, 1927)
- Talbert, George A**, Ph D, D Sc (hon) 400 Granite St, Waupaca, Wis *Professor Physiology and Pharmacology, Emeritus, U of S Dakota, Sc D U of S Dakota* (1, 1919)

- Talbot, Samuel Armstrong, A M , M S , Ph D
Wilmer Institute, Johns Hopkins Hospital,
Baltimore, Md *Instructor in Physiological
Optics, Johns Hopkins University* (1, 1940)
- Taliaferro, William H , Ph D Department of
Bacteriology, University of Chicago, Chicago,
Ill *Eliakim H Moore Distinguished Service
Professor of Parasitology and Dean of the Division
of Biological Sciences* (6, 1930)
- Tannenbaum, Albert, M D Michael Reese Hos-
pital, 29th St & Ellis Ave , Chicago, Ill *Director,
Department of Cancer Research* (4, 1942)
- Tashiro, Shiro, Ph D , M D College of Medicine,
University of Cincinnati, Cincinnati, O *Pro-
fessor of Biochemistry* (1, 1913, 2, 1913)
- Tatum, Arthur L , M S , Ph D , M D University
of Wisconsin, Madison *Professor of Pharma-
cology* (1, 1913, 3, 1919)
- Tauber, Henry, Ph D 1909 S Sixth St , Phila-
delphia, Pa *Publisher Commercial Alcohol Com-
pany, Supervisor of Ethyl Alcohol Fermentation*
(2, 1933)
- Taylor, Alonzo E , M D General Mills, Inc
200 Chamber of Commerce, Minneapolis, Minn
*Director of Research Director Emeritus, Food
Research Institute, Stanford University* (5,
1933)
- Taylor, Alton R , Ph D Duke University School
of Medicine, Durham, N C *Research Associate
in Experimental Surgery* (6, 1943)
- Taylor, Craig L , Ph D , M D Dept of Engineer-
ing, Univ of Calif , Los Angeles, Calif (1, 1945)
- Taylor, Fred A , Ph D 320 E North Ave , N S ,
Pittsburgh, Pa *Biochemist, Singer Memorial
Laboratory* (2, 1933)
- Taylor, Haywood M , M S , Ph D Duke Uni-
versity School of Medicine, Durham, N C
*Associate Professor of Biochemistry and Toxi-
cology, Biochemist and Toxicologist to Duke
Hospital* (4, 1942)
- Taylor, Henry Longstreet, Ph D University of
Minnesota, Minneapolis *Assistant Professor of
Physiology* (1, 1944)
- Taylor, John Fuller, Ph D Washington University
School of Medicine, Euclid and Kingshighway,
St Louis, Mo *Assistant Professor of Biological
Chemistry* (2, 1944)
- Taylor, M Wight New Jersey Agricultural Exper
Station, New Brunswick *Assoc Biochem in
Nutr , and Assoc Prof of Agr Biochem, Rut-
gers Univ* (5, 1944)
- Taylor, Norman Burke, M D , F R S (Can) ,
M R C S (Eng) , L R C P (Lon) , F R C S
(Edin) , F R C P (Can) University of To-
ronto, 5, Ontario, Ont , Canada *Professor of
Physiology* (1, 1922)
- Taylor, Robert D , M D Clinical Research
Division, Cleveland Foundation, Cleveland 6, O
Member (1, 1945)
- Teague, Robert S , Ph D , M D Dept of Phar-
macology and Physiology, Medical College of
Alabama, Birmingham 5, Ala *Associate Profes-
sor of Physiology and Pharmacology* (3, 1942)
- Templeton, Roy D , B S 5630 South Flores, San
Antonio, Texas (1, 1935)
- Ten Broeck, Carl, M D The Rockefeller Insti-
tute for Medical Research, Department of Ani-
mal and Plant Pathology, Princeton, N J
Member (4, 1932, 6, 1924)
- Tepperman, Jay, M D Dept of Pharmacology ,
Syracuse University School of Medicine, Syra-
cuse, N Y (1, 1944)
- Terplan, Kornel L , M D University of Buffalo,
School of Medicine, Buffalo, N Y *Professor of
Pathology* (4, 1935)
- Thannhauser, S J , M D , Ph D Pratt Diag-
nostic Hospital, 30 Bennet St , Boston, Mass
*Professor of Clinical Medicine, Tufts Medical
School, Associate Chief, Pratt Diagnostic Hos-
pital* (2, 1937)
- Thayer, Sidney Allen, Ph D 1402 S Grand
Blvd , St Louis 4, Mo *Associate Professor of
Biochemistry, St Louis University School of
Medicine* (2, 1933)
- Theiler, Max, M D Rockefeller Foundation,
New York City *Member of Field Staff* (4,
1938)
- Thienes, Clinton H , A M , M D , Ph D Uni-
versity of Southern California School of Medi-
cine, Los Angeles *Professor of Pharmacology*
(3, 1928)
- Thomas, Arthur W , Ph D Columbia University,
New York City *Professor of Chemistry* (2,
1924)
- Thomas, Byron H , M S , Ph D Iowa State Col-
lege, Ames *Professor and Head, Animal
Chemistry and Nutrition, Iowa Agricultural
Experiment Station* (5, 1933)
- Thomas, Caroline Bedell, M D The Johns Hop-
kins Hospital, Baltimore, Md *Instructor in
Medicine, Johns Hopkins University School of
Medicine* (1, 1939)
- Thomas, J Earl, M S , M D Jefferson Medical
College, Philadelphia, Pa *Professor of Physi-
ology* (1, 1922, 3, 1924)
- Thompson, Marvin R , Ph C , B Sc , M Ph ,
(Hon) Ph D 67 Greenwich Ave , Stamford,
Conn (3, 1944)
- Thompson, Randall L , Sc D , M D Medical Col-
lege of Virginia, Richmond, Va *Associate Pro-
fessor of Bacteriology* (6, 1937)
- Thompson, William R , Ph D 1 Darrock Rd ,
Delmar, N Y *Senior Biochemist, Division of
Laboratories and Research, New York State
Department of Health* (2 1934)
- Thomson, David Landsborough, M A , Ph D ,
F R S C McGill University, Montreal, Canada.

- Professor of Biochemistry and Dean of the Faculty of Graduate Studies and Research* (2, 1929)
- Thorn, George Widmer, M D** Peter Bent Brigham Hospital, Boston, Mass *Professor of Medicine of Harvard University* (1, 1939)
- Tillett, William S, M D, Sc D (hon)** Department of Bacteriology, New York University College of Medicine, 477 First Ave, New York City *Professor of Medicine* (6, 1927)
- Tilt, Jennie, M S, Ph D** Florida State College for Women, Tallahassee *Professor of Physiological Chemistry and Nutrition* (5, 1937)
- Tipson, R Stuart, Ph D** Mellon Institute of Industrial Research, University of Pittsburgh, Pittsburgh, Pa *Senior Fellow, Department of Research in Pure Chemistry* (2, 1937)
- Tipton, Samuel R, Ph D** Medical College of Alabama, Birmingham 5 *Associate Professor of Physiology and Pharmacology* (1, 1910)
- Tisdall, Frederick F, M S, M D, M R C S, L R C P (London), F R C P (C)** University of Toronto, Toronto, Canada *Assistant Professor of Pediatrics, Department of Medicine, University of Toronto, Physician, Hospital for Sick Children* (2, 1922, 5, 1933)
- Tislow, Richard, M D** Schering Corporation, Bloomfield, N J *Head of the Biology Laboratory* (1, 1944)
- Titus, Harry W, A M, Ph D** Lime Crest Research Lab, RFD #1, Newton, N J *Technical Counsellor and Director of Nutritional Research* (2, 1929, 5, 1933)
- Tobias, Julian M, M D** University of Chicago, Chicago, Ill *Instructor in Physiology On leave to Medical Research Laboratory, Edgewood Arsenal, Md* (1, 1944)
- Tocantins, Leandro Maués, M D** Jefferson Medical College, Philadelphia, Pa *Associate Professor of Medicine* (1, 1939)
- Todhunter, Elizabeth Neige, M Sc, Ph D** University of Alabama, University *Professor of Nutrition* (5, 1939)
- Toennies, Gerrit, Ph D** Lankenau Hospital Research Institute, Philadelphia, Pa *Research Chemist* (2, 1934)
- Tolle, Chester D, Ph D** Food and Drug Administration, Federal Security Agency, Washington, D C *Senior Biochemist* (5, 1942)
- Toman, James E P, Ph D** Dept ' of Pharmacology and Physiology, Univ of Utah School of Medicine, Salt Lake City (1, 1945)
- Tomlinson, Wray Joseph, M D** Fort Logan Veteran's Hospital, Denver, Colorado *Chief of Labs, Assist Prof of Pathology, Univ of Colorado School of Medicine* (4, 1945)
- Tompkins, Edna H, M D** Laboratory of Applied Physiology, Yale University, 4 Hillhouse Ave, New Haven, Conn *Research Associate, Associate Professor* (4, 1941)
- Toomey, John A, M D, LL B** Division of Contagious Diseases, City Hospital, 3395 Scranton Rd, Cleveland, O *Professor of Pediatrics (Contagious Diseases), Western Reserve University School of Medicine* (6, 1913)
- Torda, Clara, Ph D, M D** Cornell Medical Center, New York City *Research Fellow in Department of Medicine* (1, 1913, 3, 1911)
- Toth, Louis A, M S, Ph D** Dept of Physiology, Louisiana State University, Medical Center, New Orleans 13, La *Assistant Professor of Physiology* (1, 1910)
- Totter, John R, M A, Ph D** Univ of Arkansas School of Medicine, Little Rock, Ark *Associate Professor, Dept of Physiological Chemistry* (2, 1916)
- Tourtellotte, Dee, M S, D Sc** Charles B Knox Gelatin Co, 11th and Erie Sts, Camden, N J (5, 1935)
- Tower, Sarah Sheldon, M D, Ph D** Johns Hopkins Medical School, Baltimore, Md *Associate in Anatomy* (1, 1932)
- Traub, Frederick B, M D** 205 East 82nd St, New York 28, N Y *Associate Bacteriologist, Jewish Hospital of Brooklyn* (6, 1916)
- Travell, Janet, M D** Cornell University Medical College, 1300 York Ave, New York City *Instructor in Pharmacology* (3, 1933)
- Travis, Lee Edward, A M, Ph D** University of Southern California, Los Angeles *Professor of Psychology and Director of the Psychological Center, Major, YAAF (Yuma, Ariz)* (1, 1929)
- Treadwell, Carleton R, M S, Ph D** Dept of Biochemistry, George Washington University School of Medicine, 1335 H St, Washington, D C (2, 1941)
- Treffers, Henry P, Ph D** Yale Medical School, Department of Immunology, New Haven, Conn *Associate Professor of Immuno-chemistry* (6, 1942)
- Trimble, Harry C, M D, Ph D** 25 Shattuck St, Boston, Mass *Assistant Professor of Biological Chemistry, Harvard Medical School* (2, 1929, 5, 1936)
- Tuft, Louis H, M D** 1530 Locust St, Philadelphia, Pa *Assistant Professor of Medicine, Temple University Medical School, Chief of Clinic of Allergy and Applied Immunology, Temple University Hospital* (6, 1928)
- tum Suden, Caroline, M A, Ph D** 80 E Concord St, Boston, Mass *Evans Research Fellow in Physiology, Boston University School of Medicine, Assistant, Evans Memorial Staff, Massachusetts Memorial Hospitals* (1, 1936)
- Tunturi, Archie Robert, M S, Ph D** Univ of Oregon Medical School, Portland, Ore *Assistant Professor of Anatomy* (1, 1946)

- Tuohy, Edward B, M S, M D Percy Jones General Hospital, Battle Creek, Mich *Assistant Professor of Anesthesiology, Mayo Foundation Captain, M C* (3, 1941)
- Turner, Abby H, Ph D Mount Holyoke College, South Hadley, Mass *Professor of Physiology* (1, 1928)
- Turner, William A, Ph D Bureau of Dairy Industry, U S Department of Agriculture, Beltsville, Md *Associate Chemist* (2, 1929)
- Tuttle, Waid Wright, M A, Ph D State University of Iowa, Iowa City *Professor of Physiology* (1, 1925)
- Tweedy, Wilbur R, Ph D Loyola University School of Medicine, 706 S Wolcott St, Chicago, Ill *Professor and Chairman, Department of Biological Chemistry* (2, 1931)
- Tyler, David B, Ph D California Institute of Technology, Pasadena *Hixon Fund Fellow* (1, 1943)
- Unna, Klaus R W, M D 1853 W Polk St, Chicago 12, Ill *Assistant Professor, Dept of Pharmacology, Univ of Illinois Coll of Medicine* (1, 1941, 3, 1944, 5, 1942)
- Upton, Morgan, M A, Ph D Dept of Psychology, St Lawrence University, Canton, N Y *Assistant Director, British Ministry of Supply Mission, 404 A Bradford Building, 1800 K St, N W, Washington, D C* (1, 1934)
- Urban, Frank, Ph D, M D Research Hospital, University of Illinois, 1819 W Polk St, Chicago 12, Ill *Interne* (2, 1932)
- Utter, Merton F, Ph D Dept of Biochemistry, Western Reserve Univ, Cleveland, Ohio, *Associate Professor of Physiological Chemistry* (2, 1946)
- Vahlteich, Ella McCollum, M A, Ph D 46 Hudson Ave, Edgewater, N J (5, 1933)
- Van Dyke, H B, Ph D, M D 630 W 168th St, New York, N Y *Hosack Professor of Pharmacology, Columbia University, College of Physicians and Surgeons* (1, 1925, 3, 1942)
- van Harreveld, Anthonie, M A, M D California Institute of Technology, Pasadena *Associate Professor of Physiology* (1, 1941)
- Van Liere, Edward J, M S, M D, Ph D The School of Medicine, West Virginia University, Morgantown *Professor of Physiology and Dean* (1, 1927)
- Van Slyke, Donald D, Ph D, Sc D, M D Rockefeller Institute for Medical Research, 66th St and York Ave, New York City *Member, Member, National Academy of Sciences* (2, 1908)
- van Wagenen, Gertrude, Ph D Yale University School of Medicine, New Haven, Conn *Associate Professor* (1, 1932)
- van Wagtendonk, William J, Ph D Dept of Zoology, Indiana University, Bloomington, Ind *Associate Professor of Zoology* (2, 1946)
- Van Winkle, Walton, Jr, M D American Medical Assn, 535 N Dearborn St, Chicago 10, Ill (3, 1939)
- Vars, Harry M, Ph D Harrison Department of Surgical Research, University of Pennsylvania Medical School, Philadelphia *Assistant Professor of Physiological Chemistry* (2, 1935, 5, 1935)
- Velick, Sidney Frederick Dept of Biochemistry, Washington Univ School of Medicine, Euclid Ave and Kingshighway, St Louis 10, Mo *Assistant Professor of Biochemistry* (2, 1946)
- Vennesland, Birgit, Ph D Dept of Biochemistry, University of Chicago, Chicago, Ill *Assistant Professor* (2, 1944)
- Venning, Eleanor H, M S, Ph D University Clinic, Royal Victoria Hospital, Pine Ave, Montreal, Quebec, Canada *Assistant Professor of Medicine, McGill Univ* (2, 1938)
- Vestling, Carl Swensson, Ph D Noyes Lab, Univ of Illinois, Urbana, Ill *Assistant Professor of Chemistry* (2, 1946)
- Vickery, Hubert B, M S, Ph D Connecticut Agricultural Experiment Station, New Haven *Lecturer on the Chemistry of Proteins, Yale University, Biochemist in Charge, Connecticut Agricultural Experiment Station, Member, National Academy of Sciences* (2, 1923)
- Victor, Joseph, M D Research Service, First Division, Goldwater Memorial Hospital, Welfare Island New York 17 *Experimental Pathologist, Assistant Professor of Pathology, Columbia University College of Physicians and Surgeons* (4, 1935)
- Virtue, Robert W, Ph D 2134 E Iliff Ave, Denver, Colo *Associate Professor of Chemistry, University of Denver* (2, 1939)
- Visscher, Maurice B, Ph D, M D University of Minnesota, Minneapolis *Professor and Head of Dept of Physiology* (1, 1927)
- Voegtlin, Carl, Ph D University of Rochester School of Medicine and Dentistry, Rochester, N Y *Lecturer in Pharmacology* (1, 1908, 2, 1908, 3, 1908)
- von Haam, Emmerich, M D Ohio State University, Columbus *Professor of Pathology* (4, 1938)
- Von Oettingen, W F, M D, Ph D National Institute of Health, Division of Industrial Hygiene, Bethesda, Md *Principal Industrial Toxicologist* (3, 1925)
- Vorwald, Arthur J, Ph D, M D Research Division, Bureau of Medicine and Surgery, Washington, D C *Pathologist* (4, 1937)
- Vos, Bert J, Ph D, M D Division of Pharmacology, Food and Drug Administration, Washington, D C *Associate*

- Waddell, James, Ph D E I duPont de Nemours & Co, New Brunswick, N J *Director of the Biological Laboratory* (2, 1930, 5, 1935)
- Wadsworth, Augustus B, M D Manchester, Vermont (4, 1935, 6, 1920)
- Waelsch, Heinrich, M D, Ph D 722 West 168th St, New York 32, N Y *Associate Research Biochemist, N Y State Psychiatric Institute and Hospital, Assistant Professor of Biological Chemistry, Columbia University* (2, 1911)
- Wagman, Irving H, M A, Ph D Dept of Physiology, Jefferson Medical College, Philadelphia 7, Pa (1, 1946)
- Waisman, Harry A, M S, Ph D Biochemistry Bldg, University of Wisconsin, Madison *Associate in Biochemistry* (2, 1944)
- Wakeman, Alfred J, Ph D Hatfield Hill Road, Bethany, Conn *Retired* (2, 1906)
- Wakerlin, George E, Ph D, M D University of Illinois Medical School, 1853 W Polk St, Chicago *Professor of Physiology* (1, 1933, 3, 1934)
- Wakim, Khalil G, M D, Ph D University of Indiana Medical School, Bloomington *Professor of Physiology* (1, 1942)
- Wald, George, M A, Ph D Biological Laboratories, Harvard University, Cambridge, Mass (1, 1934)
- Walker, Arthur M, M D University of Pennsylvania, Philadelphia *Associate Professor of Pharmacology, Major, M C* (1, 1932, 3, 1939)
- Walker, Burnham S, Ph D, M D Boston University School of Medicine, 80 E Concord St, Boston, Mass *Professor of Biochemistry* (2, 1940)
- Walker, Ernest Linwood, S D Second and Parnassus Aves, San Francisco, Calif *Professor of Tropical Med, The George Williams Hooper Foundation for Medical Research, University of California* (3, 1931)
- Walker, Sheppard M, M A, Ph D 7339 Lindell Blvd, University City 5, Mo *Instructor in Physiology* (1, 1946)
- Wallace, George B, A M, Sc D (hon) M D 477 First Ave, New York City *Professor of Pharmacology, New York University College of Medicine* (1, 1901, 2, 1906, 3, 1909)
- Wallen-Lawrence, Zonja, Ph D 4534 W Pine Blvd, St Louis, Mo *Lecturer on Nutrition and Diet, Washington University School of Dentistry* (2, 1937)
- Walter, Annabel W 29 Perry St, New York 14, N Y *Bacteriologist, New York City Dept of Health, Bureau of Labs* (6, 1946)
- Walter, Carl W, M D Harvard Medical School, 25 Shattuck Street, Boston, Mass *Director, Laboratory for Surgical Research, Assistant Professor of Surgery, Harvard Medical School, Senior Associate in Surgery, Peter Bent Brigham Hospital* (4, 1912)
- Walters, Orville S, Ph D, M D McPherson, Kan *Physician* (1, 1936)
- Walton, Robert P, M A, Ph D, M D Medical College of the State of South Carolina, Charleston *Professor of Pharmacology* (3, 1933)
- Walton, Seth T, A M D, M S, Ph D Laboratory, Veteran's Hospital, Oteen, N C *Director of Laboratories and Research* (6, 1936)
- Walzer, Matthew, M D 20 Plaza St, Brooklyn, N Y *Attending in Allergy, Jewish Hospital of Brooklyn* (6, 1921)
- Wang, Chi Che, M S, Ph D Mayo Clinic 214 16th Ave, S W Rochester, Minn (2, 1922, 5, 1933)
- Wang, Shih-Chun, M D, Ph D Columbia University College of Physicians and Surgeons, 630 W 168th St, New York City *Assistant Professor in the Department of Physiology* (1, 1943)
- Wangeman, Clayton P, B A, M D State of Wisconsin General Hospital, 1300 University Ave, Madison 6, Wisconsin *Assistant Professor of Anesthesiology* (3, 1946)
- Wangensteen, Owen Harding, M D University of Minnesota, Minneapolis *Professor of Surgery* (4, 1931)
- Warner, Emory D, M D Medical Laboratories Bldg, Iowa City, Ia *Professor of Pathology* (4, 1937)
- Warner, Robert C, Ph D New York University College of Medicine, 477 First Ave, New York 16, N Y *Assistant Professor of Chemistry* (2, 1946)
- Warren, Charles O, Ph D, M D 405 East 72nd St, New York, N Y *Medical Associate, Commonwealth Fund* (1, 1941)
- Warren, Madeleine Field, A M, Ph D 9 High Rock St, Needham Mass Harvard School of Public Health, 55 Shattuck St, Boston, Mass *Associate in Physiology* (1, 1933)
- Warren, Shields, M D 195 Pilgrim Rd, Boston, Mass *Pathologist, New England Deaconess Hospital, Assistant Professor of Pathology, Harvard Medical School* (4, 1929)
- Wartman, William Beckman M D Northwestern Univ, 303 East Chicago Ave, Chicago 11, Ill *Professor of Pathology* (4, 1940)
- Wasteneys, Hardolph, Ph D, F R S C University of Toronto, Toronto, Canada *Professor and Head of Department of Biochemistry* (2, 1915)
- Wastl, Helene, M D Hahnemann Medical College and Hospital, Philadelphia, Pa *Research Associate, Depts of Anatomy and Therapeutics* (1, 1939)

- Waterman, Robert E, B S Schering Corporation, 86 Orange St, Bloomfield, N J *Vice-President* (2, 1940)
- Waters, Ralph Milton, M D 1300 University Ave, Madison, Wis *Professor of Anesthesia, University of Wisconsin* (3, 1937)
- Watson, Cecil J, M D, Ph D Department of Medicine, University Hospital, Minneapolis, Minn *Professor and Head of Department of Medicine* (4, 1941)
- Watson, John B, A M, Ph D, LL D 420 Lexington Ave, New York City *Vice President of the J Walter Thompson Co* (1, 1907)
- Waud, Russell A, M D, M Sc, Ph D Medical School, University of Western Ontario, London, Canada *Professor of Pharmacology* (1, 1925, 3, 1931)
- Waugh, David F, Ph D Department of Biology and Biological Engineering, Massachusetts Institute of Technology, Cambridge *Assistant Professor of Physical Biology* (1, 1943)
- Wearn, Joseph T, M D Lakeside Hospital, Cleveland, O *Professor of Medicine, Western Reserve University, Director of Medicine, Lakeside Hospital* (1, 1921)
- Weatherby, J H, M A, Ph D Dept of Physiology and Pharmacology, Medical College of Virginia, Richmond, Va *Associate Professor of Research Pharmacology* (3, 1941)
- Weber, Clarence J, M D, Ph D University of Kansas Hospitals, Kansas City *Assistant Professor of Research Medicine* (2, 1931)
- Webster, Bruce, M D, C M Cornell University Medical College, 1300 York Ave, New York City *Assistant Professor Medicine, Associate Attending Physician, New York Hospital* (5 1935)
- Weed, Lewis H, A M, M D, Sc D Johns Hopkins University Medical School, Baltimore, Md *Professor of Anatomy* (1, 1919)
- Wegria, René, M D Department of Medicine, Presbyterian Hospital, 622 W 168th St, New York City (1, 1941)
- Weichert, Charles K, Ph D University of Cincinnati, Cincinnati, O *Professor of Zoology* (1, 1935)
- Weil, Alfred J, M D Lederle Laboratories, Inc, Pearl River, N Y *Immunologist* (6, 1940)
- Weil, Arthur, M D 161 East 71st St, New York, N Y (4, 1940)
- Weil, Leopold, Ph D Eastern Regional Research Laboratory, U S Department of Agriculture, Chestnut Hill Station, Philadelphia, Pa *Chemist* (2, 1942)
- Weir, Everett G, M S, Ph D School of Medicine, Howard University, Washington, D C *Assistant Professor of Physiology* (1, 1941)
- Weiss, Charles, M S, Ph D, M D Jewish Hospital, York & Tabor Roads, Philadelphia, Pa *Director of Laboratories* (4, 1934, 6, 1920)
- Weiss, Emil, M D, Ph D P O Box 714, Chicago, Ill *Pathologist, Chicago Eye, Ear, Nose and Throat Hospital* (6, 1927)
- Weiss, Paul, Ph D University of Chicago, Chicago, Ill *Professor of Zoology* (1, 1936)
- Welch, Arnold D, Ph D, M D Western Reserve University School of Medicine, Cleveland, O *Professor and Director of Department of Pharmacology* (3, 1942, 5, 1944)
- Welch, Henry, M S, Ph D Rm 6171 S Agriculture Bldg, Washington, D C *Chief, Division of Penicillin Control and Immunology, U S Food and Drug Administration* (6, 1932)
- Weld, Charles Beecher, M A, M D Dalhousie University, Halifax, N S, Canada *Professor of Physiology* (1, 1936)
- Weld, Mrs Julia T College of Physicians and Surgeons, 630 W 168th St, New York City *Research Associate in Pathology* (6, 1920)
- Welker, William H, A C, Ph D, D Sc 1853 W Polk St, Chicago, Ill *Professor of Biological Chemistry and Head of the Department, College of Medicine, University of Illinois* (2, 1906)
- Weller, Carl Vernon, M D 1130 Fair Oaks Parkway, Ann Arbor, Mich *Professor of Pathology and Chairman, Department of Pathology, University of Michigan* (4, 1923)
- Wells, Herbert S, M D University of Minnesota Minneapolis 14 *Professor of Clinical Physiology* (1, 1932)
- Wells, Joseph Albert, M S, Ph D Northwestern University Medical School, Chicago, Ill *Associate in Pharmacology* (3, 1944)
- Welsh, John H, Ph D Biological Laboratories, Harvard University, 16 Divinity Ave, Cambridge 38, Mass *Associate Professor of Zoology* (1, 1945)
- Wendel, William B, Ph D Department of Biochemistry, Tulane University, 6501 St Charles Ave, New Orleans 15, La *Professor of Biochemistry* (2, 1932)
- Werkman, C H, Ph D Science Hall, Iowa State College, Ames *Professor and Head of Department of Bacteriology* (2, 1942)
- Werle, Jacob M, M D, Capt, 138 Evacuation Hospital, A P O 408, New York, N Y (1, 1943)
- Werner, Harold W, Ph D The Wm S Merrell Co, Lockland Station, Cincinnati, O *Director of Pharmacology Research* (3, 1942)
- Werthenberger, Grace E, S M Ph D Women's Medical College of Pennsylvania Philadelphia *Assistant Professor of Physiology* (1, 1943)
- Werthessen, Nicholas T, Ph D Shrewsbury, Mass *Worcester Foundation for Experimental Biology, Research Staff* (1, 1946)
- Wesson, Laurence Goddard, Ph D Forsyth

- Dental Infirmary, Boston, Mass *Research Biochemist* (2, 1929, 3, 1932)
- West, Edward S, M S, Ph D University of Oregon Medical School, Portland *Professor of Biochemistry* (2, 1925)
- West, Harold D, M S, Ph D Meharry Medical College, Nashville 8, Tenn *Professor of Biochemistry and Head of Dept of Biochemistry* (2, 1946)
- West, Randolph, M A, M D 622 W 168th St, New York City *Associate Professor of Medicine, Columbia University* (2, 1931)
- Westerfeld, Wilfred Wiedey, Ph D Syracuse University College of Medicine, Syracuse 10, N Y *Professor of Biochemistry* (2, 1944)
- Weymouth, Frank W, Ph D Stanford University, Calif *Professor of Physiology and Executive of the Department* (1, 1917)
- Wheeler, George W, M D New York Hospital, 525 E 68th St, New York City *Assistant Director* (6, 1920)
- Wheeler, Kenneth M, Ph D Bureau of Laboratories, Connecticut State Department of Health, 1179 Main St, Hartford *Research Microbiologist* (6, 1938)
- Wheeler, Mary W, M A Division of Laboratories and Research, New York State Department of Health, Albany *Associate Bacteriologist* (6, 1933)
- Wheeler, Ruth, Ph D Vassar College, Poughkeepsie, N Y *Professor Emeritus of Physiology and Nutrition* (2, 1915, 5, 1933)
- Wheelon, Homer, M S, M D American Bank Bldg, Seattle, Wash (1, 1919)
- Whipple, George H, M D, Sc D University of Rochester, Rochester, N Y *Professor of Pathology and Dean of the School of Medicine and Dentistry, Member of the National Academy of Sciences* (1, 1911, 4, 1913)
- White, Abraham, M A, Ph D 333 Cedar St, New Haven, Conn *Associate Professor of Physiological Chemistry, Yale University* (2, 1934, 5, 1937)
- White, Florence R, M A, Ph D National Cancer Institute, Bethesda 14, Md *Biochemist, National Institute of Health* (2, 1946)
- White, Frank D, Ph D, F I C Medical College, University of Manitoba, Winnipeg, Canada *Assistant Professor of Biochemistry, Faculty of Medicine* (2, 1931)
- White, Harvey Lester, M D *Associate Professor of Physiology, Washington University Medical School, St Louis, Mo* (1, 1923)
- White, Julius, A M, Ph D National Cancer Institute, Bethesda, Md *Senior Biochemist* (2, 1937)
- White, Paul Dudley, M D, Massachusetts General Hospital, Boston *Lecturer in Medicine, Harvard Medical School, Physician (in charge of Cardiac Clinics and Laboratory), Mass General Hospital* (3, 1921)
- Whitehead, Richard W, M A, M D University of Colorado School of Medicine, 4200 E Ninth Ave, Denver *Professor of Physiology and Pharmacology* (1, 1933, 3, 1928)
- Wiener, Alexander S, M D 61 Rutland Rd, Brooklyn, N Y *Bacteriologist and Scrologist to Office of Chief Medical Examiner of New York City, Head of Transfusion Division, Jewish Hospital of Brooklyn* (6, 1932)
- Wiersma, Cornelis A G, M A, Ph D California Institute of Technology, Pasadena *Associate Professor of Physiology* (1, 1911)
- Wiggers, Carl J, M D, Sc D Medical School, Western Reserve University, Cleveland, O *Professor and Director of Physiology* (1, 1907, 3, 1909)
- Wiggers, Harold C, Ph D College of Medicine, University of Illinois, 1853 W Polk St, Chicago *Associate Professor of Physiology* (1, 1938)
- Wigodsky, Herman S, Ph D, M D AAF School Aviation Medicine, Randolph Field, Texas *Chief, Dept of Physiology* (1, 1943)
- Wikler, Abraham, M D U S Public Health Service Hospital, Lexington, Ky *Surgeon (R), U S Public Health Service* (3, 1944)
- Wilde, Walter S, Ph D Carnegie Institution of Washington, Department of Embryology, Wolfe and Madison Sts, Baltimore 5, Md *Junior Investigator, Assistant Professor of Physiology* (1, 1944)
- Wilder, Russell M, Ph D, M D Mayo Clinic, Rochester, Minn *Professor of Medicine, Mayo Foundation, University of Minnesota* (1, 1921, 4, 1924, 5, 1933)
- Wiley, Frank H, M S, Ph D Food and Drug Administration, Federal Security Agency, Washington 25, D C *Chemist* (2, 1933)
- Wilhelme, Jane Russell, Ph D Yale University School of Medicine, 333 Cedar St, New Haven, Conn *Instructor in Physiological Chemistry* (1, 1939)
- Wilhelm, Alfred E, Ph D 333 Cedar St, New Haven, Conn Yale University School of Medicine *Assistant Professor of Physiological Chemistry* (2, 1942)
- Wilhelm, Charles Martel, M D Creighton University School of Medicine, Omaha, Neb *Professor of Physiology* (1, 1931)
- Wilkerson, Vernon A, M D, Ph D Howard University Medical School, Washington, D C *Professor and Head of Department of Biochemistry* (2, 1936)
- Williams, Edwin G, M D, D T M, D T H National Institute of Health, Bethesda 14, Md *Senior Surgeon U S Public Health Service,*

- Director of Research, U S P H S Hospital, Lexington, Ky (3, 1944)
- Williams, Harold H., Ph D Department of Biochemistry, Cornell University, Ithaca, N Y, Professor of Biochemistry (2, 1938, 5, 1936)
- Williams, Horatio B., M D, Sc D Box 893, Greenwich, Conn Dalton Professor of Physiology Emeritus, Columbia University (1, 1912)
- Williams, J W., M S, Ph D University of Wisconsin, Chemistry Bldg, Madison Professor of Chemistry (2, 1944)
- Williams, Ray D., M S, M D 6834 Waterman St, St Louis, Mo Assistant Professor of Clinical Medicine, Washington University (5, 1941)
- Williams, Robert Hardin, M D Thorndike Laboratory, Boston City Hospital, Boston, Mass Associate in Medicine, Harvard Medical School, Assistant Physician, Thorndike Memorial Laboratory, Junior Visiting Physician, II and IV Medical Services (Harvard) Boston City Hospital (4, 1940)
- Williams, Robert R., M S, D Sc 297 Summit Ave, Summit, N J Chemical Consultant, Bell Telephone Laboratories (2, 1919, 5, 1941)
- Williams, Roger J., Ph D, D Sc University of Texas, Department of Chemistry, Austin Professor of Chemistry, Director, Biochemical Institute (2, 1931, 5, 1945)
- Wills, J H., M S, Ph D Dept of Pharmacology, Univ of Tennessee, Memphis 3, Tenn (1, 1943)
- Wilson, David Wright, M S, Ph D University of Pennsylvania Medical School, Philadelphia Benjamin Rush Professor of Physiological Chemistry (1, 1915, 2, 1915)
- Wilson, Frank N., M D University Hospital, Ann Arbor, Mich Professor of Medicine, University of Michigan (4, 1925)
- Wilson, Karl M., M D University of Rochester, School of Medicine, Rochester, N Y Professor of Obstetrics and Gynecology (4, 1927)
- Wilson, P W., Ph D Department of Agricultural Bacteriology, University of Wisconsin, Madison Professor in Agricultural Bacteriology (2, 1939)
- Wilson, Robert H., Ph D U S Dept of Agriculture, Western Regional Research Laboratory, 800 Buchanan St, Albany, Calif Pharmacologist (3, 1937)
- Winder, Claude V., Sc D 1927 Dexter Ave, Ann Arbor, Mich Pharmacologist, Parke, Davis & Company, Detroit, Mich (1, 1938)
- Windle, William Frederick, Ph D Medical School, University of Washington, Seattle, Wash Professor of Anatomy (1, 1937)
- Winkenwerder, Walter LaF., M D 1014 St Paul St Baltimore, Md Associate in Medicine, Johns Hopkins Medical School (6, 1938)
- Winkler, Alexander Woodward, A M, M D New Haven Hospital, 789 Howard Ave, New Haven, Conn Assistant Professor of Medicine, Yale University School of Medicine (1, 1940)
- Winnick, Theodore, Ph D Division of Biochemistry, Univ of California, Berkeley, Calif Research Associate (2, 1946)
- Winter, Charles A., Ph D University of Oklahoma, School of Medicine, 801 E 13th St, Oklahoma City Associate Professor of Physiology (1, 1940)
- Winter, Irwin Clinton, Ph D, M D G D Searle & Co, P O Box 5110, Chicago 80, Ill Director of Clinical Research (3, 1941)
- Winters, Jet C., M A, Ph D University of Texas, Austin Professor of Home Economics (5, 1933)
- Winternitz, M C., M D Yale University School of Medicine, New Haven, Conn Anthony N Brady Professor of Pathology (4, 1913)
- Wintersteiner, Oskar, Ph D The Squibb Institute for Medical Research, New Brunswick, N J Head Division of Organic Chemistry, Honorary Professor of Biochemistry Rutgers University (2, 1930)
- Wintrobe, Maxwell Myer, M D, Ph D University of Utah School of Medicine, Salt Lake City Professor and Head of the Department of Internal Medicine (4, 1940)
- Winzler, Richard J., Ph D Dept of Biochemistry, Univ of Southern Calif Medical School, Los Angeles 7, Calif Assistant Professor of Biochemistry (2, 1946)
- Wiseman, Bruce Kenneth, M D Kinsman Hall, Ohio State University, Columbus Professor and Chairman of Department of Medicine, Assistant Director of Medical Research (4, 1932)
- Wislocki, George B., M D Harvard University Medical School, 25 Shattuck St, Boston, Mass Parkman Professor of Anatomy (1, 1924)
- Witebsky, Ernest, M D Buffalo General Hospital, 100 High St, Buffalo, N Y Professor of Bacteriology and Immunology (6, 1935)
- Wittich, Fred W., M D 401 LaSalle Medical Bldg Minneapolis 2, Minn Sec-Treas American College of Allergists, Chairman, Executive Committee, International Association of Allergists (6, 1944)
- Witzemann, Edgar J., M A, Ph D Service Memorial Building, University of Wisconsin, Madison Associate Professor of Physiological Chemistry (2, 1925)
- Wolbach, S Burt, M D Harvard University Medical School, 25 Shattuck St, Boston, Mass Shattuck Professor of Pathological Anatomy, Member, National Academy of Sciences (4, prior to 1920)
- Wolf, Arnold Veryl, Ph D Albany Medical College, Albany, N Y Assistant Professor of Physiology and Pharmacology (1, 1946)

- Wolff, Harold G , M D , M A New York Hospital, 525 E 68th St , New York City *Associate Professor of Medicine, Cornell University Medical College, Associate Attending Physician, New York Hospital* (1, 1930, 3, 1912)
- Wood, Earl H , M S , Ph D , M D Mayo Aeromedical Unit, Mayo Foundation, Rochester, Minn *Assistant in Physiology* (1, 1913)
- Wood, Harland G , Ph D Department of Biochemistry, Western Reserve University, Cleveland, Ohio *Professor of Biochemistry* (2, 1914)
- Wood, Horatio C , Jr , M D , Ph M 319 S 41st St , Philadelphia, Pa *Professor of Pharmacology and Therapeutics, University of Pennsylvania, Professor of Materia Medica Philadelphia College of Pharmacy and Science* (3, 1908)
- Woodbury, Robert A , Ph D , M D University of Georgia, School of Medicine, Augusta *Professor of Pharmacology* (1, 1936, 3, 1941)
- Woodruff, Lorande Loss, A M , Ph D Yale University, New Haven, Conn *Professor of Protozoology, Member, National Academy of Sciences* (1, 1910)
- Woods, Alan C , M D Wilmer Institute, Johns Hopkins Hospital, Baltimore, Md *Ophthalmologist-in-Chief, Acting Professor of Ophthalmology, Johns Hopkins University, Director, Wilmer Ophthalmological Institute* (6, 1918)
- Woods, Ella, A.M , Ph D University of Idaho, Moscow *Home Economist, Experiment Station* (2, 1925, 5, 1933)
- Woodward, Alvalyn E , M S , Ph D University of Michigan, Ann Arbor *Assistant Professor of Zoology* (1, 1932)
- Woodyatt, Rollin T , M D 237 E Delaware Place, Chicago, Ill *Professor of Medicine, Rush Medical College, University of Chicago* (2, 1912)
- Woolley, D Wayne, Ph D Rockefeller Institute for Medical Research, 66th St , and York Ave , New York City *Associate Member* (2, 1946, 5, 1941)
- Woolsey, Clinton N , M D Johns Hopkins University School of Medicine, Baltimore, Md *Associate in Physiology* (1, 1938)
- Wright, Angus, M D University of Southern California Medical School, 657 S Westlake Ave , Los Angeles *Pathologist, California Hospital* (4, 1935)
- Wright, Arthur W , M D Albany Medical College, New Scotland Ave , Albany, N Y *Professor of Pathology and Bacteriology* (4, 1941)
- Wright, Charles Ingham, M S , Ph D National Institute of Health, Bethesda, Md *Senior Pharmacologist, U S Public Health Service* (1, 1935, 3, 1936)
- Wright, George G , Ph D Div of Infectious Diseases, National Inst of Health, Bethesda, Md *National Research Fellow* (6, 1943)
- Wright, Harold N , M S , Ph D University of Minnesota, Minneapolis *Associate Professor of Pharmacology* (3, 1933)
- Wright, Lemuel D , Ph D Medical Research Division, Sharp and Dohme, Inc , Glenholden, Pa *Research Biochemist* (2, 1916, 5, 1916)
- Wright, Sydney L , M A , Ph D Endsmeet Farm, Glenside, Pa (2, 1933)
- Wulzen, Rosalind, M S , Ph D Oregon State College, Corvallis *Assistant Professor of Zoology* (1, 1916)
- Wyckoff, Ralph W G , Ph D U S Public Health Service, National Institute of Health, Bethesda, Md *Senior Scientist* (6, 1910)
- Wyman, Jeffries, Jr , Ph D Biological Laboratories, Harvard University, Cambridge, Mass *Associate Professor of Zoology* (1, 1928)
- Wyman, Leland C , Ph D Boston University School of Medicine, Boston, Mass *Associate Professor of Physiology* (1, 1927)
- Wynne, Arthur M , M A , Ph D , F R S C Department of Biochemistry, University of Toronto, Toronto, Canada *Professor of Biochemistry* (2, 1940)
- Yerkes, Robert M , Ph D Yale Laboratories of Primate Biology, 333 Cedar St , New Haven, Conn *Professor of Psychobiology, Yale University, Member of the National Academy of Sciences* (1, 1904)
- Yonkman, Frederick F , Ph D , M D Ciba Pharmaceutical Products, Inc , Summit, N J *Chief Pharmacologist* (3, 1931)
- Youmans, William Barton, M A , Ph D , M D University of Oregon Medical School, Portland *Professor of Physiology* (1, 1939)
- Young, A G , Ph D , M D 520 Commonwealth Ave , Boston, Mass *Assistant Professor of Therapeutics, Boston University School of Medicine, Medical Director, Corey Hill Hospital, Brookline* (3, 1925)
- Young, E G , Ph D , F R S C Dalhousie University, Halifax, N S , Canada *Professor of Biochemistry* (2, 1925)
- Youngburg, Guy E , M S , Ph D 66 Park Circle, Eggertsville, Buffalo, N Y *Professor of Biological Chemistry, University of Buffalo* (2, 1927)
- Yuile, Charles L , M D , C M University of Rochester School of Medicine and Dentistry, 260 Crittenden Blvd , Rochester, N Y *Associate Professor of Pathology* (4, 1941)
- Zechmeister, L California Institute of Technology, Pasadena *Professor of Organic Chemistry* (2, 1941)
- Zeckwer, Isolde T , M D School of Medicine, University of Pennsylvania, Philadelphia *Assistant Professor of Pathology* (1, 1934, 4, 1927)
- Zeldis, Louis Jenrette, M D Emory University School of Medicine, Atlanta, Ga *Assistant Professor of Pathology* (4, 1945)

Zimmerman, Harry M, M D Montefiore Hospital, Gun Hill Rd, New York 67, N Y (4, 1933)
 Zittle, Charles A, Ph D Biochemical Research Foundation, Newark, Delaware (2, 1946)
 Zweifel, Benjamin W, Ph D Department of Biology, New York University, Washington

Square, New York 3, N Y Research Associate (1, 1945)
 Zwemer, Raymond L, Ph D 5003 Battery Lane, Bethesda 14, Md College of Physicians and Surgeons, Columbia University, 630 W 168th St, New York City Assistant Professor of Anatomy On leave Dept of State, Washington, D C (1, 1930)

SUMMARY OF MEMBERSHIP

The American Physiological Society	955
The American Society of Biological Chemists	714
The American Society for Pharmacology and Experimental Therapeutics	340
The American Society for Experimental Pathology	304
The American Institute of Nutrition	303
American Association of Immunologists	282
Total Members by Societies	2898

DECEASED MEMBERS

- Abel, John J (1, 2, 3) May 26, 1938
 Abbott, A C (1) September 11, 1936
 Abramson, H L (6) April, 1934
 Adams, J George (2) August 29, 1926
 Adler, Herman M (2) December 6, 1935
 Adler, Isaac (3) February 2, 1912
 Alsberg, Carl L (1, 2) October 31, 1940
 Apfelbach, Carl Wesley (4) June 25, 1943
 Armsby, H P (1) October 19, 1921
 Atkinson, Harry V (3) May 7, 1939
 Atwater, W O (1) September 22, 1907
 Austin, William C (2) November 20, 1935
 Bancroft, F W (1) August 23, 1924
 Banting, F G (3) February 21, 1941
 Banzhaf, Edwin J (2, 6) March 17, 1931
 Barbour, Henry Gray (1, 2, 3) September 23, 1943
 Barkan, Georg (3) March 7, 1945
 Benedict, Stanley R (1, 2) December 21, 1936
 Bergmann, Max (2) November 7, 1944
 Beyer, Henry G (1) December 9, 1918
 Black, Otis Fisher (2) October 14, 1933
 Blackfan, Kenneth D (5) November 5, 1941
 Bleile, Albert M (1) August 16, 1933
 Bodansky, Meyer (2) June 14, 1941
 Bowditch, Henry P (1) March 13, 1911
 Braman, Winfred W (5) March 24, 1937
 Brodie, Maurice (6) May 9, 1939
 Brodie, Thomas G (1, 2) August 20, 1916
 Brown, Aaron (6) January 24, 1945
 Brown, Wade H (3, 4) August 4, 1942
 Brubaker, Albert P (1) April 29, 1943
 Bull, Carroll G (6) May 30, 1931
 Bullock, Jesse G M (3, 6) November 9, 1943
 Burget, G E (1) June 4, 1938
 Burnett, Theo C (1) 1946
 Busch, Fred C (1) January 3, 1914
 Callison, William E (3) February 26, 1937
 Calvery, Herbert O (2, 3) September 23, 1945
 Cannon, Walter B (1) October 1, 1945
 Carrel, Alexis (1, 4) November 5, 1944
 Cattell, J McKeen (1) January 20, 1944
 Chapman, Henry C (1) September 7, 1909
 Chillingworth, F P (1) June 30, 1938
 Chittenden, Russell H (1, 2, 5) December 6, 1943
 Clark, Admont Halsey (1) October 13, 1918
 Clark, Earl P (2) November 7, 1943
 Clark, G P (1) September 1, 1907
 Clarke, J Alexander (6) 1943
 Cleghorn, Allen M (1) March 20, 1916
 Cohen, Seymour J (3) June 11, 1942
 Connor, Charles L (4) June 12, 1941
 Cook, Frank C (2) June 19, 1923
 Cooley, Thomas B (5) October 13, 1945
 Coombs, Helen C (1, 3) March 4, 1944
 Coulter, Calvin B (4) May 10, 1940
 Crawford, Albert C (3) March 14, 1921
 Crile, George W (1, 3) January 7, 1943
 Cullen, Glenn E (2, 5) April 11, 1940
 Curtis, John G (1) September 20, 1913
 Cushing, Harvey (1, 4) October 7, 1939
 Cushny, A R (1) February 25, 1926
 Dalton, J C (1) February 12, 1889
 Dastré, A (1h) October 25, 1917
 D'Aunoy, Joseph Rigney (4) September 17, 1941.
 Davis, Alice Rohde (2) August 22, 1933
 Dawson, Martin H (4) April 27, 1945
 Dawson, Wilfred T (1, 3) September 19, 1939
 Denis, Willey (1, 3) January 9, 1929
 Donaldson, Henry H (1) January 24, 1938
 Dooley, David H (1) April 11, 1927
 Dreyer, George P (1) February 27, 1931
 Dunham, Edward K (2) April 16, 1922
 Dusser de Barenne, J G (1, 3) June 9, 1940
 Eaton, Alonzo Guy (1) March 9, 1946

- Edmunds, Charles W (1, 3) March 1, 1911
Englemann, Th W (1h) May 20, 1909
Ets, Harold N (1, 3) June 25, 1913
Evans, William E, Jr (3) May 6, 1916
Ewing, Ephraim MacDonald (1) August 27, 1925
Fine, Morris S (2, 5) August 15, 1916
Fitch, Richard H (1, 3) January 7, 1939
Fitz, George W (1) October 28, 1934
Flexner, Simon (6) May 2, 1946
Folin, Otto (1, 2, 3) October 26, 1934
Foster, Nellis Barnes (2) August 20, 1933
Franz, Shepherd Ivory (1) October 14, 1933
Gager, C Stuart (2) August 9, 1943
Gardner, Leroy U (4) November, 1916
Gates, Frederick L (3, 4) June 17, 1933
Gay, Frederick P (4, 6) July 14, 1939
Goodale, George L (1) April 12, 1923
Gortner, Ross A (2) September 30, 1942
Greeley, A W (1) May 15, 1904
Gross, Louis (4) October 17, 1937
Hall, G Stanley (1) April 24, 1924
Halsted, William S (4) September 7, 1922
Hammersten, O (1h) September 21, 1932
Harding, Victor John (2) July 10, 1934
Hare, Hobart Amory (1) June 15, 1931
Harrop, George A (2) August 4, 1945
Haskins, Howard Davis (1, 2) November 19, 1933
Hatcher, Robert A (1, 2, 3) April 1, 1944
Hawkins, James A, (1, 2) July 26, 1937
Henderson, Lawrence J (1, 2) February 10, 1942
Henderson, Velyien E (1, 3) August 6, 1945
Henderson, Yandell (1, 2, 3) February 19, 1944
Herter, C H (1) December 5, 1910
Hess, Alfred Fabian (2, 5) December 5, 1933
Hewlett, Albion Walter (1, 3, 4) November 10, 1925
Hirschfelder, Arthur D (1, 2, 3) October 11, 1942
Hiss, Philip H, Jr (2, 3) February 27, 1913
Hogland, Charles L (1, 5, 6) August 2, 1946
Hofmeister, F (1h) July 26, 1922
Hooker, Donald Russell (1, 3) August 1, 1946
Hooper, Charles Warren (1) January 27, 1936
Hough, Theodore (1) November 30, 1924
Howell, William H (1, 2) February 6, 1945
Howland, John (2) June 20, 1926
Huber, G Carl (1) December 26, 1934
Hyde, Roscoe R (6) September 15, 1943
Inman, Ondess L (2) July 21, 1942
Jackson, Holmes C (1, 2) October 25, 1927
Jaffe, Hermann R (4, 6) December 17, 1937
James, Wm (1) August 26, 1910
Jenkins, Oliver P (1) January 9, 1935
Jones, Frederic S (4) October 19, 1934
Jones, Walter (1, 2) February 28, 1935
Jordan, Edwin O (1) September 2, 1936
Joseph, Don R (1, 3) July 9, 1928
Julianelle, Louis A (6) August 12, 1944
Kahn, Max (2) April 8, 1926
Karr, Walter G (2) September 16, 1946
Kastle, Joseph H (1, 2) September 24, 1916
King, Walter L (6) May 1, 1936
Klotz, Oskar (4) November 3, 1936
Koch, Waldemar (3) February 2, 1912
Koessler, Karl K (2, 4, 6) February 13, 1928
Koller, C (3h) March 21, 1911
Krause, Allen K (4) May 12, 1941
Kriss, Max (5) November 15, 1911
Krumwiede, Charles (6) December 29, 1930
Landsteiner, Karl (4, 6) June 26, 1913
Langley, J N (1) November 5, 1925
Langworthy, Charles F (2) March 3, 1932
Lee, Frederic S (1) December 11, 1939
Leech, Paul Nicholas (3) January 11, 1911
Levene, Phoebus A (1, 2) September 6, 1940
Levin, Isaac (1) June 19, 1915
Lewis, Dean (1) October 9, 1911
Lewis, Paul A (3, 4, 6) June 30, 1929
Lingle, D J (1) November 27, 1936
Loeb, Jacques (1, 2) February 11, 1924
Loevenhart, A S (1, 2, 3) April 20, 1929
Lombard, Warren P (1) July 13, 1939
Long, John H (2) June 11, 1918
Lothrop, Alfred P (2) July 6, 1911
Lusk, Graham (1, 2, 5) July 18, 1932
Lyon, Elias P (1) May 4, 1937
Macallum, Archibald Byron (1, 2) April 5, 1934
Macleod, John James Richard (1) March 16, 1935
MacNeal, Ward J (4) August 15, 1946
McCordock, Howard A (4) November 13, 1938
McDonald, Claude H (1) November 18, 1944
McGlone, Bartgis (1) November 10, 1941
McKinley, Earl B (4, 6) July 28, 1938
Maes, Julian P (1) August 7, 1946
Magnus, Rudolf (3) July 25, 1927
Mall, Franklin P (1) November 17, 1917
Mallory, F B (4) September 28, 1941
Mandel, John A (1, 2) May 5, 1929
Mann, Gustav (1) July 18, 1921
Marriott, W McKim (2, 5) November 11, 1936
Marshall, John (1, 2) January 5, 1925
Martin, Ernest Gale (1) October 17, 1934
Martin, H Newell (1) October 27, 1896
Matson, Ray W (6) September, 1934
Mathews, Samuel A (1, 3) February 19, 1928
Maximow, Alexander A (4) December 4, 1928
Maxwell, S S (1) January 28, 1939
Meigs, Edward B (1, 2, 5) November 5, 1940
Mellus, E Linden (1) December 17, 1923
Meltzer, S J (1, 2, 3, 4) November 7, 1920
Mendel, Lafayette B (1, 2, 3, 5) December 9, 1935
Meyer, Hans H (3h) October 6, 1939
Miller, Elmer S (2) June 11, 1941
Miller, Joseph L (1, 3) August 6, 1937
Mills, Thomas W (1) February 13, 1915
Minot, Charles S (1) November 19, 1914
Mitchell, S Weir (1) January 4, 1914
Moore, Lillian Mary (1) August 1, 1929
Morris, J Lucien (2) March 19, 1926
Moyer, Laurence S (2) June 8, 1942

- Myers, Harold B (3) March 16, 1937
 Neuhausen, Benj S (2) August 20, 1923
 Nelson, Louis (3) April 14, 1912
 Nichols, Henry J (4) September 2, 1927
 Noguchi, Hideyo (4, 6) May 21, 1928
 Osborne, Thomas Burr (1, 2) January 29, 1929
 Osler, Sir William (1) December 29, 1919
 Ott, Isaac (1, 3) January 1, 1916
 Palmer, Albert H (2) April 10, 1945
 Palmer, LeRoy S (2, 5) March 8, 1944
 Park, William H (4, 6h) April 6, 1939
 Pavlov, Ivan P (1h) February 27, 1936
 Pearce, Richard M, Jr (4) February 16, 1930
 Perla, David (4, 6) June 14, 1940
 Peters, H C (1) July 13, 1942
 Pettibone, C J V (2) March 8, 1929
 Pfaff, Franz (1, 2) September 26, 1926
 Pfluger, E (1h) March 17, 1910
 Pincussen, Ludwig (2) November 30, 1941
 Plant, Oscar H (1, 3) October 1, 1939
 Prince, Alexander L (1) May 25, 1938
 Raiziss, George W (2) July 17, 1945
 Ralls, James O (2) December 29, 1944
 Ranson, S W (1) August 30, 1942
 Ray, George B (1) July 6, 1945
 Rees, Maurice H (1) May 25, 1945
 Reichert, Edward T (1) December 25, 1931
 Richards, Herbert M (2) January 9, 1928
 Robertson, T Brailsford (2) January 27, 1930
 Robinson, George Henry (4) September 29, 1945
 Rockwood, Elbert W (2) July 17, 1935
 Rosenbloom, Jacob (2) September 25, 1923
 Rose, Mary Schwartz (1, 2, 5) February 1, 1941
 Ross, Ellison, L (2, 3) December 21, 1938
 Roth, Paul (1, 5) November 6, 1946
 Rowe, Allan Winter (1, 2, 5) December 6, 1934
 Rutan, Robert F (2) February 19, 1930
 Salant, William (1, 2, 3) December 10, 1943
 Schafer, Sir Edward Sharpey (1h) March 29, 1935
 Schiff, Fritz (6) 1940
 Schlutz, F W (2, 5) March 8, 1944
 Schmidt, Carl L A (2) February 23, 1946
 Schoenheimer, Rudolf (2) September 11, 1941
 Scott, J M Duncan (1) January 28, 1930
 Sedgwick, William T (1) January 26, 1921
 Sellards, Andrew Watson (4) December 1, 1942
 Sewall, Henry (1) July 8, 1936
 Shaw, Louis A (1) August 27, 1940
 Sheldon, Ralph L (1) July 9, 1918
 Shohl, Alfred T (2, 5) March 25, 1946
 Shorey, Edmund C (2) January 30, 1939
 Simon, Charles E (1, 2) November 8, 1927.
 Sinclair, A N (6) October 21, 1930
 Simpson, G E (2) December 23, 1927
 Simpson, Sutherland (1) March 2, 1926
 Smith, H E (1) October 9, 1933
 Smith, R Meade (1) 1919
 Smith, Theobald (4h, 6) December 10, 1934
 Spaeth, Reynold A (1) January 26, 1925
 Spencer, Henry James (5) 1944
 Sternberg, G M (1) November 3, 1915
 Stevens, Herman C (1) May 27, 1934
 Stewart, Colin C (1) January 22, 1944
 Stewart, G N (1, 3, 4) May 28, 1931
 Stiles, Percy G (1) July 5, 1936
 Storey, Thomas A (1) October 27, 1943
 Straub, Walther (3) October 22, 1944
 Straus, Henry W (6) 1937
 Tait, John (1) October 21, 1944
 Terry, Oliver P (1) December 6, 1933
 Thatcher, Roscoe Wilfred (2) December 6, 1933
 Thompson, Wm G (1) October 27, 1927
 Torrey, John C (6) October 7, 1946
 Trask, James D (6) May 24, 1942
 Underhill, Frank P (1, 2, 3) June 28, 1932
 Van Slyke, Lucius L (2) September 30, 1931
 Vaughan, Victor C (1, 4) October 21, 1929
 Vincent, S (1) December 31, 1933
 Von Brucke Ernest T (1) June 12, 1941
 von Voit, C (1h) January 31, 1908
 Waddell, J A (3) June 8, 1945
 Wallace, Edward W (3) July 11, 1943
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INDEX

ABSTRACTS, Biochemistry, 118

—, Corrections, 265

—, Immunology, 211

—, Nutrition, 228, 261

—, Pathology, 217

—, Pharmacology, 161, 261

—, Physiology, 1, 263

—, Subject index, 257

—, Regulations for the preparation of, 510

Ac on in relation to man, effects of, 327

— F Survey of Physiology, 108, 432

meeting, Chicago, 1947, 138

tic City Meeting, notes, 266

ALDES, E J See **WOOD, LAMBERT, BALDES AND CODE**, 327

BALL, E G Chemical and nutritional observations on malarial parasites grown in vitro, 397

BARD, P Survey of Physiology, introduction, 407

BAZETT, H C, Chairman Symposium Physiological contributions to war problems, 318

BOUDREAU, F G AND R M WILDER Food and Nutrition Board, National Research Council, Review, 267

BOVARNICK, M R See **HELLERMAN, BOVARNICK AND PORTER**, 400

BOYD, T E Survey of Physiology, 422

BURTON, A C Clothing and heat exchanges, 344

CHEMOTHERAPY, bacterial, 304

Chemotherapy of Malaria, 1941-45, 298

CLARK, W M, Chairman, Symposium Biochemistry of malarial parasites, 390

Clothing and heat exchanges, 344

CODE, C F See **Wood, Lambert, Baldes and Code**, 327

COMROE, J H, JR Survey of Physiology, 428

CUSHING, J E See **Emerson and Cushing**, 379

DIETARY allowances, human, 277

Dow, P Survey of Physiology, 417

ELVEHJEM, C A Significance and limitations of food composition tables, 280

EMERSON, S AND J E CUSHING Sulfonamide antagonism of Neurospora, 379

EVANS, E A, JR Enzyme systems operating within the malarial parasite, 390

FOOD composition tables, significance and limitations of, 280

Food and Nutrition Board, National Research Council, Review, 267

GILMAN, A Therapeutic applications, chemical warfare agents, 255

GRIFFITHS, M I Shock, physiological contributions to the problem of, 351

HARTLINE, H K Visual physiology during the war, problems of, 351

High altitude problems in aviation, 319

HELLERMAN, L, M R BOVARNICK AND C C PORTER Metabolism of the malarial parasite, 400

HOOVER, DONALD RUSSELL, 313, 339

HOUTMAN, M B See **MITCHELL AND HOUTMAN**, 370

INSECTICIDES and rodenticides, 292

Interim report, American Physiological Society, 311

—, American Society of Biological Chemists, 315

—, American Society for Experimental Pathology, 315

—, The American Institute of Nutrition, 316

—, American Society for Pharmacology and Experimental Therapeutics, Inc., 137

International food-evaluation activities and problems, 270

Ivy, I C High altitude problems in aviation, 319

JEANS, P C Human dietary allowances, 277

KRAUSS, W E Nutritional aspects of the milk supply, 273

LAMBERT, E H See **WOOD, LAMBERT, BALDES AND CODE**, 327

MALARIAL Parasites, biochemistry of, 390

—, enzyme systems, 390

—, grown in vitro, 397

—, metabolism of, 400

—, naphthaquinone in metabolism, 406

MARSHALL, E K, JR Chemotherapy of malaria, 1941-45, 298

MAYNARD, L A International food-evaluation activities and problems, 270

McELROY, W D AND H K MITCHELL Neurospora, enzyme studies on a temperature sensitive mutant of, 376

Members, 463

—, deceased, 537

—, honorary, 463

MITCHELL, H K , Chairman, Symposium Neuro-
 + spora biochemistry, 361
 —, AND M B HOULIHAN *Neurospora crassa*,
 adenine requiring mutants of, 370
 —+ See McELROY AND MITCHELL, 376
 MOLITOR, H Bacterial chemotherapy, 304

NEUROSPORA, bioassay, 366
 —, biochemical tool, 362
 —, biochemistry, recent trends, 361
 —, enzyme studies, 376
 —, sulfonamide antagonism, 379
 — *crassa*, adenine-requiring mutants of, 370
 Nutritional aspects of the milk supply, 273

PHILIPS, F S Insecticides and rodenticides,
 292

Physiological contributions to war problems, 318
 Physiology in North America, survey, introduc-
 tion, 407
 —, careers and incentives of physiologists, 428
 —, economics, 422
 —, future physiology, 432
 —, identification and analysis of the North
 American population of Physiologists, 417
 —, purposes and methods of study, 408
 PORTER, C C See HELLERMAN, BOVARNICK AND
 PORTER, 400

RICHARDS, A N , Chairman, Symposium
 Advances in pharmacology resulting from war
 research, 285

ROSE, W C , Chairman, Symposium Newer
 knowledge of nutrition, 267

RYAN, F J Application of *Neurospora* to bio-
 assay, 366

SHOCK, physiological contributions to the
 problem of, 354

Sulfonamide antagonism of *neurospora*, 379

TATUM, E L *Neurospora* as a biochemical
 tool, 362

Therapeutic applications of chemical warfare
 agents, 285

VISUAL physiology during the war, problems
 of, 351

WENDEL, W B Influence of Naphthaqui-
 nones upon the respiratory and carbohydrate
 metabolism of malarial parasites, 406

WILDER, R M See BOUDREAU AND WILDER, 267

WOOD, E H , E H LAMBERT, E J BALDES AND
 C F CODE Acceleration in relation to
 aviation, 327